1-1-2006

The adverse health and psychological consequences of cannabis dependence

Wayne Hall
University of Queensland

Nadia Solowij
University of Wollongong, nadia@uow.edu.au

The adverse health and psychological consequences of cannabis dependence

Abstract

People who become dependent on cannabis are more likely than infrequent users to experience any of the adverse health effects that are caused by chronic cannabis use. Dependent cannabis use is rare in comparison with the more prevalent pattern of experimental and intermittent use (Bachman *et al.*, 1997), but it may nonetheless affect as many as 1% of adults in the USA and Australia in any 1 year (Anthony *et al.*, 1994; Hall *et al.*, 1999a). Dependent cannabis users typically smoke two or more cannabis cigarettes a day over periods of years or decades in a minority of cases (Copeland *et al.*, 2001; Solowij, 2002; Swift *et al.*, 1998b).

This chapter summarizes the most probable adverse health effects that cannabis-dependent persons are at increased risk of experiencing. With few exceptions (e.g., Solowij *et al.*, 2002; Taylor *et al.*, 2000), the literature does not directly assess the adverse health effects of cannabis dependence. The most probable effects can nonetheless be inferred from the more common studies of the effects of long-term daily cannabis use because many daily users are dependent on cannabis (Swift *et al.*, 1998a, 2001). The chapter reviews evidence on the adverse health effects of more or less daily use over periods of years during young adulthood, and among those who seek treatment in their mid-thirties who have used cannabis more or less daily for the past 15–20 years.

Keywords

adverse, health, psychological, consequences, cannabis, dependence

Disciplines

Arts and Humanities | Life Sciences | Medicine and Health Sciences | Social and Behavioral Sciences

Publication Details

Hall, W. & Solowij, N. (2006). The adverse health and psychological consequences of cannabis dependence. In R. Roffman & R. S. Stephens (Eds.), Cannabis Dependence: Its Nature, Consequences and Treatment (pp. 106-128). Cambridge: Cambridge University Press.

5

The Adverse Health and Psychological Consequences of Cannabis Dependence

WAYNE HALL AND NADIA SOLOWIJ

People who become dependent on cannabis are more likely than infrequent users to experience any of the adverse health effects that are caused by chronic cannabis use. Dependent cannabis use is rare in comparison with the more prevalent pattern of experimental and intermittent use (Bachman *et al.*, 1997), but it may nonetheless affect as many as 1% of adults in the USA and Australia in any 1 year (Anthony *et al.*, 1994; Hall *et al.*, 1999a). Dependent cannabis users typically smoke two or more cannabis cigarettes a day over periods of years or decades in a minority of cases (Copeland *et al.*, 2001; Solowij, 2002; Swift *et al.*, 1998b).

This chapter summarizes the most probable adverse health effects that cannabis-dependent persons are at increased risk of experiencing. With few exceptions (e.g., Solowij *et al.*, 2002; Taylor *et al.*, 2000), the literature does not directly assess the adverse health effects of cannabis dependence. The most probable effects can nonetheless be inferred from the more common studies of the effects of long-term daily cannabis use because many daily users are dependent on cannabis (Swift *et al.*, 1998a, 2001). The chapter reviews evidence on the adverse health effects of more or less daily use over periods of years during young adulthood, and among those who seek treatment in their mid-thirties who have used cannabis more or less daily for the past 15–20 years. These effects are organized in approximate order of prevalence and confidence that the relationship is causal (Hall & Babor, 2000a).

Assessing Health Effects of Chronic Cannabis Use

A major difficulty in appraising the adverse health effects of chronic cannabis use is a dearth of good epidemiological evidence on the long-term health consequences of cannabis use, and problems in interpreting the evidence that is available (Hall & Pacula, 2003; Hall *et al.*, 1999b). Much of the evidence comes

from North America, although more work is beginning to be reported from Australia (e.g., Swift *et al.*, 1998a), the Netherlands (e.g., van Os *et al.*, 2002), and New Zealand (e.g., Fergusson *et al.*, 2000), where there are relatively high rates of cannabis use among young adults.

The value of these epidemiological studies is often weakened by difficulties in excluding alternative explanations of associations observed between cannabis use and adverse health outcomes (Hall *et al.*, 1999b). Heavy cannabis use, for example, is correlated with alcohol and tobacco use, both of which adversely affect health in ways that may be difficult to distinguish from the effects of cannabis (e.g., respiratory disease and motor vehicle accidents). These interpretative issues are highlighted in the following review.

The Respiratory Risks of Cannabis Smoking

Over the past two decades, cross-sectional and longitudinal studies in the USA have shown that people who are regular smokers of cannabis but not tobacco have more symptoms of chronic bronchitis than non-smokers (see Tashkin, 1999, for a review). The immunological competence of the respiratory system in people who only smoke cannabis is also impaired, increasing their susceptibility to infectious diseases, such as pneumonia (Tashkin, 1999).

A prospective study was recently conducted by Taylor *et al.* (2000, 2002) who studied symptoms of respiratory disease and respiratory function in 1037 New Zealand youths 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. After adjusting for the effects of tobacco use, it was found that cannabis-dependent subjects had higher rates of wheezing, shortness of breath, chest tightness, and morning sputum production in comparison to non-smokers. The effects of cannabis dependence on respiratory symptoms were "generally similar to and occasionally greater than for tobacco smokers of 1–10 cigarettes/day" (Taylor *et al.*, 2000, p. 1673). A significantly higher proportion of cannabis-dependent subjects also had evidence of impaired respiratory function. The adverse effects of tobacco and cannabis smoking were additive.

Taylor *et al.* (2002) reported a follow-up of this cohort to age 26 years in which analyses were undertaken of the cumulative effects of cannabis on respiratory function (objectively assessed by forced expiratory volume and vital capacity). The study assessed cannabis use at ages 18, 21, and 26 years, and carefully controlled for the effects of cigarette smoking assessed at the same ages. The heaviest cannabis users (900 or more occasions of use by age 26 years) had

2.6–7% reductions in lung function. The authors argued that given the short time frame of the follow-up, "the trend suggests that continued cannabis smoking has the potential to result in clinically important impairment of lung function" (p. 1055).

In very long-term cannabis users who are also often regular tobacco smokers, cannabis smoking appears to exacerbate the adverse respiratory effects of tobacco smoking (Tashkin, 1999). For example, half of the participants who had smoked cannabis for 20 years studied in Australia reported symptoms of chronic bronchitis (Swift *et al.*, 1998b) and most of these were or had also been regular tobacco smokers. This was double the rate of symptoms reported by their age peers who did not smoke cannabis.

Chronic Cannabis Use and Respiratory Cancers

Cannabis smoking could be a cause of cancer if tetrahydrocannabinol (THC) or the substances generated when cannabis is burnt produced genetic mutations in somatic cells exposed to cannabis smoke (such as those in the lung). There is only weak evidence that THC is "mutagenic" in this sense (MacPhee, 1999). THC can produce changes in cellular processes in animal cells in the test tube, altering cell metabolism, DNA synthesis, and cell division (MacPhee, 1999). These changes, however, probably delay or stop cell division rather than produce cellular changes that may lead to cancer (MacPhee, 1999). There is no evidence that THC and other cannabinoids produce mutations in microbial assays used to assess mutagenicity, such as the Ames test (MacPhee, 1999; Marselos & Karamanakos, 1999). Indeed, there is some evidence that THC and other cannabinoids may have anti-tumor activity in cell cultures and in animals (Guzman, 2003).

Cannabis *smoke* is mutagenic in the test tube, and hence is a potential carcinogen (Marselos & Karamanakos, 1999). Cannabis smoke produces chromosomal aberrations, is mutagenic in the Ames test, and causes cancers in the mouse skin test (MacPhee, 1999). The fact that cannabis smoke is carcinogenic suggests that any cancers caused by cannabis smoking are most likely to occur in organs that receive long-term exposure to carcinogens in cannabis smoke, such as the lungs, the aerodigestive tract (mouth, tongue, esophagus), and the bladder (Hall & MacPhee, 2002).

There are good reasons for suspecting that cannabis may cause cancers of the lung and the aerodigestive tract (Hall & MacPhee, 2002). First, tobacco is a cause of respiratory cancer and cannabis smoke contains many of the same carcinogens as tobacco smoke (Marselos & Karamanakos, 1999). Second, chronic

cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers (Tashkin, 1999).

Cancers have been reported in the aerodigestive tracts of young adults who have been chronic cannabis smokers (Donald, 1991; Taylor, 1988). In many cases, members of this group were also cigarette smokers and alcohol consumers, but Caplan and Brigham (1990) reported two cases of cancer of the tongue in men aged 37 and 52 years who neither smoked tobacco nor 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, and cannabis exposure has been assessed retrospectively, knowing that the user has cancer.

Sidney *et al.* (1997) studied cancer incidence during an 8.6-year follow-up of 64,855 members of the Kaiser Permanente Medical Care Program. Participants were asked about cannabis use during medical screening (average age 33 years) between 1979 and 1985 and followed up for 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. There were no more cases of cancer at follow-up when those who had ever used cannabis and current cannabis users were compared to those who had never 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 (relative risk, RR = 3.1), and so did males who were current cannabis smokers (RR = 4.7).

Zhang *et al.* (1999) 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 a 2.6 odds ratio (OR) for cannabis smoking after adjusting for cigarette smoking, alcohol use, and other 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 (OR = 3.1).

Two recent studies of oral squamous cell carcinoma have failed to find any association between cannabis use and oral cancers. Llewellyn *et al.* (2004) reported a case–control study of 116 cases (identified from a cancer register) and 207 age and sex matched controls (sampled from the same general practices as the cases). They failed to find any association between self-reported cannabis use and oral cancers in young adults but they only compared people who had

used cannabis heavily (10% of the sample) with the majority who reported no use and the prevalence of cannabis use was low.

Rosenblatt *et al.* (2004) reported a more convincing null finding in a larger community-based study of 407 cases and 615 controls aged 18–65 years in Washington state. They found no relationship between the risk of oral squamous cell carcinoma and various indices of cannabis use, including ever versus never used, frequency of use, and duration. They argued that the Zhang *et al.* (1999) study findings arose from bias introduced by the use of blood donors as controls. The prevalence of cannabis use was lower than it should have been among controls, thereby producing a spurious association. By contrast, the prevalence of cannabis use among the controls in Rosenblatt *et al.*'s study was exactly that predicted from population surveys of cannabis use in the USA adult population.

The conflicting findings mean that it is unclear what the risk of oral cancer is among cannabis smokers. The risk appears to be small when compared to those of tobacco and alcohol, especially given the modest increase in RR observed in the only positive study and the good statistical power in the study that failed to detect an association of this size (Rosenblatt *et al.*, 2004). There is also uncertainty about whether the risks of cannabis smoking interact with those of alcohol and tobacco, which many cannabis users also use. Larger cohort studies and larger, well-designed case–control studies of cancers are needed to clarify the relationship between cannabis smoking and cancer risk. These risks may become clearer as the baby boomer birth cohorts (who were the first to smoke cannabis in any numbers) enter the age groups in which cancer incidence begins to rise steeply (Hall & MacPhee, 2002; Rosenblatt *et al.*, 2004).

Chronic Cannabis Use and Brain Function

Cannabis exerts its most prominent effects on the central nervous system where it acts on an endogenous cannabinoid system that is involved in regulating mood, emotion, memory, attention, and other cognitive functions (Solowij, 1998). Recent animal research has established that cannabinoid receptors play a role in memory storage and retrieval processes (see Iversen, 2003; Piomelli, 2003; Solowij, 2002). The findings from both human and animal research suggest that prolonged use of cannabis alters the functioning of the brain's cannabinoid system but that this does not translate to serious impairment (for recent reviews of the literature, see Ameri, 1999; Solowij, 1999, 2002).

Evidence for structural brain damage in humans following prolonged exposure to cannabis has generally not been sustained (see Solowij, 1998, 1999 for reviews). A recent study used sophisticated measurement techniques to show

that frequent but relatively short-term use of cannabis produces neither structural brain abnormalities nor global or regional changes in brain tissue volume or composition that are assessable by magnetic resonance imaging (MRI) (Block *et al.*, 2000a). More recent research has found reduced cortical gray matter and increased white matter in those who commenced using cannabis before the age of 17 years compared to those who started using later (Wilson *et al.*, 2000). The possibility that there may be greater neurotoxic and adverse hormonal and developmental effects of cannabis use in adolescence deserves further attention in research.

A number of studies have demonstrated altered brain function and metabolism in humans following acute and chronic use of cannabis using cerebral blood flow (CBF), positron emission tomography (PET), and electroencephalographic (EEG) techniques. In the most recent carefully controlled study, Block and colleagues (2000b) found that after more than 26 h of supervised abstinence, frequent cannabis users (17 times per week for approximately 4 years) showed substantially lower resting levels of brain blood flow (up to 18%) than controls in a large region of posterior cerebellum and in prefrontal cortex. Similarly, Lundqvist *et al.* (2001) showed lower mean hemispheric and frontal blood flow shortly after cessation of cannabis use. These changes may have direct or indirect effects on cognitive function.

Loeber and Yurgelun-Todd (1999) have proposed that chronic cannabis use results in changes at the cannabinoid receptors that affect the dopamine system. This, in turn, produces a global reduction in brain metabolism, particularly in the frontal lobe and cerebellum. Recent research is increasingly using functional imaging techniques to examine brain activation during the performance of cognitive tasks (e.g., Porrino *et al.*, 2004; Smith *et al.*, 2004; Solowij *et al.*, 2004). Preliminary studies have shown diminished activity in the brains of chronic marijuana users relative to controls, even when the cannabis users abstained from cannabis for 28 days prior to testing (Block *et al.*, 2002; Loeber & Yurgelun-Todd, 1999).

Chronic Cannabis Use and Cognitive Impairment

Cognitive impairments, particularly short-term memory deficits, are reported by many cannabis-dependent persons who seek help to cease using cannabis, and are often given as one of the main reasons for wanting to stop using cannabis (Solowij, 1998). The evidence from controlled studies, however, indicates that long-term heavy use of cannabis does not appear to produce severe or grossly debilitating impairment of cognitive function like that produced by chronic

heavy alcohol use (Solowij, 1998). There is, nonetheless, evidence that long-term or heavy cannabis users show more subtle types of cognitive impairment that are detected in well-controlled studies using sensitive measures.

A major concern with earlier studies of the cognitive effects of chronic cannabis use was that cannabis users might have had poorer cognitive functioning than controls before they started to use cannabis (Solowij, 1998). Recent studies have addressed this problem by matching users and non-users on estimated premorbid intellectual functioning (Solowij, 1998) or on test performance prior to the onset of cannabis use (Block & Ghoneim, 1993; Block *et al.*, 2002; Pope & Yurgelun-Todd, 1996). These studies have found cognitive impairments associated with frequent and/or long-term cannabis use. Frequent users (using at least 7 times per week for 2 years) showed impairment in tests assessing verbal expression, mathematics, and memory (Block & Ghoneim, 1993; Block *et al.*, 2002). Heavy users (using at least 22 of the past 30 days) were more susceptible to interference, made more perseverative errors, had poorer recall, and showed deficient learning compared to light users (who had used no more than 9 times in the past month) (Pope & Yurgelun-Todd, 1996).

Solowij *et al.* (2002) found few impairments when comparing the neuropsychological performance of dependent, heavy cannabis users (near daily) with an average 10 years of regular use to a non-user control group. Heavy users with an average 24 years of regular use, however, showed impaired attention and a generalized memory deficit with impaired verbal learning, retention, and retrieval. Both groups of users showed impaired temporal judgment. In a series of earlier studies, Solowij (1998) used more sensitive measures of brain function (event-related potentials) to demonstrate attentional impairments in shorter-term users (5+ years). In every study, Solowij found that impairment increased with the number of years of cannabis use (Solowij, 1998; Solowij *et al.*, 2002).

While specific deficits in verbal learning, memory, and attention continue to be the most consistently replicated impairments in this population, the deficits are variously attributed to duration of cannabis use (Solowij *et al.*, 2002), frequency of cannabis use (Pope *et al.*, 2001), or cumulative dosage effects (Bolla *et al.*, 2002). The differential effects of the various parameters of cannabis use (frequency, duration, and dose) have not been investigated consistently, and debate continues about whether these deficits should be attributed to lingering acute effects, drug residues, abstinence effects, or gradual changes occurring in the brain as a result of cumulative exposure to cannabis (Pope *et al.*, 1995; Solowij, 1998, 2002; Solowij *et al.*, 2002).

Research continues to investigate the propensity for recovery of cognitive functioning following cessation of cannabis use. Solowij (1998) found partial

recovery following a median 2 years abstinence (range 3 months–6 years) in a small group of ex-users performing a selective attention task. Sensitive brain event-related potential measures, however, continued to show impaired information processing that was correlated with the number of years of cannabis use. Bolla *et al.* (2002) found persistent dose-related decrements in neurocognitive performance after 28 days abstinence in heavy young users (mean age 20, 5 years use). Pope *et al.* (2001) reported that memory impairments may recover after 28 days abstinence from cannabis, while in another report based on the same sample (Pope *et al.*, 2002), they found that verbal and memory deficits persisted in those who had commenced cannabis use prior to the age of 17 years but not in those who started later in life. Subjects were between the ages of 30 and 55 years at the time of the study. This finding accords with other findings of adverse effects in those commencing regular cannabis use before versus after the age of 17 years (Ehrenreich *et al.*, 1999; Wilson *et al.*, 2000). Further research is needed to elucidate the impact of cannabis use on the developing brain.

The hippocampus, prefrontal cortex, and cerebellum are major sites of endogenous cannabinoid activity and strongly implicated in the cognitive impairments associated with chronic cannabis use. Functional brain imaging studies hold promise for further investigation of the parameters of cannabis use that are associated with specific short- or long-lasting cognitive deficits and the neurocognitive concomitants of dysfunction (e.g., Porrino *et al.*, 2004; Smith *et al.*, 2004; Solowij *et al.*, 2004).

Lyketsos *et al.* (1999) have reported the only large-scale prospective epidemiological study of the effect of cannabis use on cognitive functioning. They assessed cognitive decline on the Mini Mental State Examination (MMSE) in 1318 adults over 11.5 years. They found no relationship between cannabis use and decline in MMSE score, and this persisted when adjustments were made for age, sex, education, minority status, and use of alcohol and tobacco. The Lyketsos *et al.* study is consistent with other evidence that cannabis use does not produce *gross* cognitive impairment (Solowij, 1998), but for the following 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 who were not followed up had poorer MMSE scores at first assessment. Second, the MMSE is a screening test for gross cognitive impairment. It tests a restricted set of very simple cognitive functions and it is, therefore, not sensitive to smaller changes in specific cognitive functions. Third, any effect of cannabis use may have been diluted by the inclusion among "heavy users" of people who reported smoking daily or more often for over 2 weeks during any one of the study wave

periods. Since cannabis use declines steeply with age (Bachman *et al.*, 1997), few in this sample were likely to be daily cannabis users for any length of time.

Accidental Injury and Chronic Cannabis Use

Cannabis intoxication produces dose-related impairments in cognitive and behavioral performance, slowing reaction time and information processing, impairing perceptual-motor coordination and motor performance, short-term memory, attention, signal detection, tracking behavior, and time perception (Hall *et al.*, 1994; Solowij, 1998; Ramaekers *et al.*, 2004). These effects increase with the dose of THC, and are larger and more persistent in tasks that require sustained attention (Chait & Pierri, 1992; Hall *et al.*, 1994).

It has been unclear until recently whether these impairments increase the risk of motor vehicle accidents in most cannabis users (Hall *et al.*, 2001). Studies of the effects of cannabis upon on-road driving performance, for example, found modest impairments (Smiley, 1999) as cannabis-intoxicated persons drive more slowly and take fewer risks than alcohol-intoxicated drivers, probably because they are more aware of their psychomotor impairment than alcohol-affected drivers (Smiley, 1999). Epidemiological evidence on the role of cannabis use in fatal motor vehicle accidents had also been equivocal because blood levels of the cannabinoids often studied did not indicate whether a driver or pedestrian was intoxicated at the time of an accident (see Hall *et al.*, 2001 for a review). Moreover, many drivers with cannabinoids in their blood also have a high blood alcohol level at the time of the accident (Hall *et al.*, 2001). The fact that cannabis was rarely found on its own in motor vehicle fatalities was consistent with the epidemiological evidence that cannabis is often used with alcohol (e.g., Hall *et al.*, 2001). The separate effects of alcohol and cannabis on psychomotor impairment and driving performance were approximately additive (Chesher, 1995).

More recent evidence supports an increased risk of accidents among cannabis users who drive. Gerberich *et al.* (2003) analyzed the relationship between self-reported cannabis use and hospitalization for accidental injury in a cohort of 64,657 patients from a Health Maintenance Organization (HMO). Current cannabis users had higher rates of all-cause injury, self-inflicted injury, motor vehicle accidents, and assaults than former cannabis users or non-users, in both men and women. These relationships persisted for all-cause injury after controlling for other variables including alcohol and tobacco use among both men (RR = 1.28) and women (RR = 1.37). The relationships for motor vehicle accidents (RR = 1.96) and assault (RR = 1.90) persisted after statistical adjustment

among men but not among women, reflecting much lower rates of both cannabis use and accidents in women than men in the cohort.

Mura *et al.* (2003) reported a case–control study of the relationship between THC and its metabolites in the serum of 900 persons hospitalized for injuries sustained in motor vehicle accidents and 900 controls of the same age and sex admitted to the same French hospitals for reasons other than trauma. The proportion with THC in their sera was higher in cases (10%) than controls (5%) (OR = 2.5). The highest proportion was found among those under the age of 27 years. They did not statistically adjust for blood alcohol level in these analyses but in 60% of their cases THC was found alone.

The convergence of recent evidence suggests that cannabis does increase the risk of motor vehicle crashes (Ramaekers *et al.*, 2004). Studies that have measured THC in blood (rather than inactive metabolites that reflect past use) have found a dose–response relationship between THC and risk of accident. The combination of THC and alcohol produces more marked impairment and increased accident risk (Ramaekers *et al.*, 2004).

Cardiovascular Effects

The most consistent physiological effect of cannabis in humans and animals is to increase heart rate (Chesher & Hall, 1999; Jones, 2002). This change parallels the experienced "high" and is related to amount of THC in the blood (Chesher & Hall, 1999). The hearts of healthy young adults are only mildly stressed by these effects (Institute of Medicine, 1999; Jones, 2002; Sidney, 2002). An increased heart rate is most obvious in occasional cannabis users because users become tolerant to these effects of THC within 24 h in laboratory studies and, in some cases, even large amounts of cannabis had little effect on heart rate (Chesher & Hall, 1999; Jones, 2002). The development of tolerance to these effects has also been observed in field studies of chronic heavy cannabis users in Costa Rica, Greece, and Jamaica. These studies failed to find any evidence of cardiac toxicity related to cannabis use (Chesher & Hall, 1999).

There are a number of concerns about the effects of cannabis use on patients with ischemic heart disease, hypertension, and cerebrovascular disease (Jones, 2002; Sidney, 2002). These include the possibilities of cardiac arrhythmias, chest pain, and myocardial infarction (heart attack). As THC has analgesic effects, it may mask chest pain, delaying treatment seeking. Cannabis smoking also increases the level of carboxyhaemoglobin in the blood, decreasing oxygen delivery to the heart, increasing the work of the heart and, perhaps, the risk of atheroma formation (Jones, 2002). Patients with cerebrovascular disease may

also experience strokes caused by changes in blood pressure and patients with hypertension may experience exacerbations of their disease for the same reason (Chesher & Hall, 1999).

Mittleman *et al.* (2001) reported a case-crossover study to assess whether smoking cannabis may trigger an acute myocardial infarction. They asked 3882 patients who had had a myocardial infarction in the previous 4 days about their use of marijuana in the day on which it occurred. They compared this with the rate of cannabis use on another recent day when they had not had an infarct. Cannabis use was found to increase 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 time course of the effects that THC and carbon monoxide have on heart function. Mittleman *et al.* estimated that a 44-year-old adult who used cannabis daily would increase their annual risk of an acute cardiovascular event by 1.5–3%.

The findings of this study are consistent with laboratory studies that have found that smoking cannabis cigarettes adversely affects patients with heart disease. Aronow and Cassidy (1974) compared the effect of smoking a cannabis and a high nicotine 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 (1975) 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 *et al.* (1977).

Special Populations of Cannabis-Dependent Persons

The Educational Consequences of Adolescent Cannabis Dependence

Adolescents who initiate cannabis use in their early teens are more likely to become regular cannabis users and are more likely to discontinue a high school education and to experience job instability in young adulthood (Hall & Pacula, 2003a; Lynskey & Hall, 2000). The strength of these relationships in cross-sectional studies is reduced in longitudinal studies when account is taken of the fact that adolescents who are heavy cannabis users have lower academic aspirations and poorer high school performance prior to using cannabis than do their peers who do not use at the same age (Hall & Pacula, 2003a; Lynskey & Hall, 2000).

A causal interpretation of the link between early cannabis use and subsequent educational performance has been supported by studies that have statistically controlled for a range of variables on which cannabis users and non-users differ prior to their cannabis use (e.g., Fergusson & Horwood, 1997, 2000; Macleod *et al.*, 2004). In these and other studies, early cannabis use predicts an increased risk of cannabis dependence, early school leaving, and precocious transitions to adult roles by engaging in early sexual activity, unplanned parenthood during adolescence, unemployment, and leaving the family home early (Hall & Pacula, 2003a; Hall *et al.*, 2001; Lynskey & Hall, 2000). Fergusson *et al.* (2003a) attribute the lower educational achievement in young people to the effects of the social context in which cannabis is used, rather than any specific effect of cannabis itself on intellectual ability or motivation. It is still possible that poorer cognitive functioning might contribute to poor school performance and hence to early school leaving.

The Gateway Hypothesis

Research on drug use in adolescence and adulthood among American adolescents in the 1970s has consistently found a regular pattern of initiation into the use of illicit drugs in which cannabis use typically follows alcohol and tobacco use and precedes the use of stimulants and opioids (Hall & Lynskey, 2003; Hall *et al.*, 2001).

The interpretation of this sequence of drug initiation remains controversial (Hall & Lynskey, 2003b). Some argue that the pattern arises because the pharmacological effects of cannabis increase the likelihood of using more hazardous drugs later in the sequence, a hypothesis for which there is some supportive animal evidence (Hall & Lynskey, 2003b). There is also support for two other hypotheses that are not mutually exclusive:

1. that there is a selective recruitment into cannabis use of non-conforming adolescents who have a propensity to use a range of intoxicating substances, including other illicit drugs;
2. that once recruited to dependent cannabis use, the regular social interaction with drug using peers and the illicit drug market increases the likelihood of their using other illicit drugs (Hall *et al.*, 2001).

When compared to non-using peers, adolescents who start cannabis use early and become daily cannabis users are at a higher risk of using other illicit drugs (Fergusson & Horwood, 1997, 2000; Fergusson *et al.*, 2002). This increased risk is attributed to factors that are in place even before the cannabis use begins

(i.e., family backgrounds and school performance), in addition to the finding that early users are more likely to keep company with other drug using peers (Fergusson & Horwood, 2000). Nonetheless, the better-controlled longitudinal studies show that heavy cannabis use in adolescence predicts an increased risk of using "harder" drugs that persists after controlling for pre-existing differences between adolescents who do and do not use cannabis (Fergusson & Horwood, 2000; Fergusson *et al.*, 2002; Hall & Lynskey, 2003b).

One possibility is that this unexplained association is due to uncontrolled factors, such as a genetic vulnerability to become dependent on a variety of different 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 (Heath, 1995), cannabis (Kendler & Prescott, 1998), and tobacco (Han *et al.*, 1999). More importantly, a component of the genetic vulnerability to dependence on these three drug classes is shared or common (True *et al.*, 1999), and so are the shared family and environmental factors that influence alcohol and cannabis dependence (Lynskey *et al.*, 1998; True *et al.*, 1999).

The hypothesis of common genes for regular use of cannabis and other illicit drugs has been directly tested using a discordant twin design by Lynskey *et al.* (2003). In this study, Lynskey *et al.* examined the relationship between cannabis and other illicit drug use in 311 monozygotic (136) and dizygotic (175) Australian twin pairs in which one twin had and the other twin had not used cannabis before the age of 17 years. If the association was attributable to a shared environment, then discordant twins raised together should not differ in the use of other illicit drugs. Similarly, if the association was attributable to a shared genetic vulnerability to drug dependence, then there should be no difference in the use of other illicit drugs between monozygotic twins who did and did not use cannabis before the age of 17 years. Lynskey *et al.* found that the twin who had used cannabis before the age of 17 years was more likely to have used sedatives, hallucinogens, stimulants, and opioids than their co-twin who had not used cannabis before the age of 17 years. Twins who had used cannabis were also more likely to report symptoms of abuse or dependence on cannabis and other illicit drugs than their twin who did not. These relationships persisted after controlling for other non-shared environmental factors that predicted an increased risk of developing drug abuse or dependence.

The findings of Lynksey *et al.* (2003), when taken together with those of Fergusson and Horwood (2000), suggest that shared genes and/or shared environment explain a substantial part of the association between cannabis use and other illicit drug use. The size of the association in the study of twins after statistical adjustment was substantially smaller (RR ~ 2–4) than that reported in the study of Fergusson and Horwood (2000) (RR ~ 59) but this may reflect in part the cruder measure of cannabis use in the Lynskey *et al.* study.

Psychosis and Schizophrenia

Until recently, the most convincing evidence that cannabis use precipitates schizophrenia came from a 15-year prospective study of cannabis use and schizophrenia in 50,465 Swedish conscripts (Andreasson *et al.*, 1987). Andreasson *et al.* found that those who had tried cannabis by age 18 years were 2.4 times more likely to receive a diagnosis of schizophrenia than those who had not. The likelihood of receiving a diagnosis of schizophrenia increased with the number of times cannabis had been used. Compared to those who had not used cannabis, the risk of developing schizophrenia was 1.3 times higher for those who had used cannabis 1–10 times, 3 times higher for those who had used cannabis between 1 and 50 times, and 6 times higher for those who had used cannabis more than 50 times. These risks were substantially reduced after statistical adjustment for variables that were related to the risk of developing schizophrenia but they nevertheless remained statistically significant. Compared to those who had never used cannabis, those who had used cannabis 1–10 times were 1.5 times more likely, and those who had used 10 or more times were 2.3 times more likely to receive a diagnosis of schizophrenia.

Zammit *et al.* (2002) reported a 27-year follow-up of the Swedish cohort study. Zammit *et al.* found a dose–response relationship between frequency of cannabis use at baseline and risk of schizophrenia during the follow up and demonstrated that the relationship between cannabis use and schizophrenia persisted when they statistically controlled for the effects of other drug use and other potential confounding factors, including a history of psychiatric symptoms at baseline. They estimated that 13% of cases of schizophrenia could be averted if all cannabis use were prevented (i.e., the attributable risk of cannabis to schizophrenia was 13%). The relationship was a little stronger in cases observed in the first 5 years, probably reflecting the decline in cannabis use that occurs with age.

Zammit *et al.*'s (2002) findings have been supported by a study conducted by van Os and colleagues (2002). This was a 3-year longitudinal study of the relationship between self-reported cannabis use and psychosis in a community sample of 4848 people in the Netherlands. van Os *et al.* substantially replicated the Swedish cohort in a number of important ways. First, cannabis use at baseline predicted an increased risk of psychotic symptoms during the follow-up period in individuals who had not reported psychiatric symptoms at baseline. Second, there was a dose–response relationship between frequency of cannabis use at

baseline and risk of psychotic symptoms during the follow up period. Third, the relationship between cannabis use and psychotic symptoms persisted when they statistically controlled for the effects of other drug use. Fourth, the relationship between cannabis use and psychotic symptoms was stronger for cases with more severe psychotic symptoms. van Os *et al.* estimated the attributable risk of cannabis to psychosis was 13% for psychotic symptoms and 50% for cases with psychotic disorders adjudged to need psychiatric treatment. Fifth, those who reported any psychotic symptoms at baseline were more likely to develop schizophrenia if they used cannabis than were individuals who were not so vulnerable.

These findings have been replicated in two smaller New Zealand cohort studies. Arseneault *et al.* (2002) reported a prospective study of the relationship between adolescent cannabis use and psychosis in young adults in a New Zealand birth cohort ($N = 759$) whose members had been assessed on risk factors for psychotic symptoms and disorders since birth. Arsenault *et al.* found a relationship between cannabis use by age 15 years and an increased risk of psychotic symptoms by age 26 years. So too did Fergusson *et al.* (2003b), who have reported a longitudinal study of the relationship between cannabis dependence at age 18 years and the number of psychotic symptoms reported at age 21 years in the Christchurch birth cohort in New Zealand. They found that cannabis dependence at age 18 years predicted an increased risk of psychotic symptoms at age 21 years (RR of 2.3). This association was smaller but still significant after adjustment for potential confounds (RR of 1.8).

In all of these studies, the relationship between cannabis use and the timing of the onset of psychotic symptoms was uncertain. Subjects were assessed once a year or less often and reported retrospectively on their cannabis use during the preceding year. Moreover, cannabis use was often only assessed by the number of times that cannabis had been used or the number of times used per week or month. A recent French study examined the relationship between cannabis use and psychotic symptoms in more detail using an experience sampling method (Verdoux *et al.*, 2002). These investigators asked 79 college students to report on their drug use and experience of psychotic symptoms at randomly selected time points, several times each day, over 7 consecutive days. The students gave their ratings after being randomly prompted to do so by a signal sent to a portable electronic device that they carried. The students were a stratified sample from a larger group in which high cannabis users ($N = 41$) and students identified as vulnerable to psychosis ($N = 16$) were over-represented. Verdoux *et al.* found that in time periods when cannabis was used, users reported more unusual perceptions. In vulnerable individuals, cannabis use was more strongly associated with strange impressions and unusual perceptions than in individuals who lacked this vulnerability. There was no relationship between reporting unusual experiences and using cannabis, as would be expected if self-medication were involved.

A major epidemiological puzzle, given this evidence, is that the treated incidence of schizophrenia, particularly early onset acute cases, has declined (or remained stable) during the 1970s and 1980s despite very substantial increases in cannabis use among young adults in Australia and North America (Hall & Degenhardt, 2000b). Although there are complications in interpreting such trends, a large reduction in treated incidence has been observed in a number of countries which have a high prevalence of cannabis use and in which the reduction is unlikely to be a diagnostic artifact (Hall, 1998; Degenhardt *et al.*, 2003).

A number of retrospective and prospective studies that have controlled for confounding variables give evidence that cannabis use exacerbates the symptoms of schizophrenia (e.g., Linszen *et al.*, 1994). In Australia, a third of persons with schizophrenia and other psychoses have been found to be daily users of cannabis (Jablensky *et al.*, 2000), a much higher rate than the 2% reported in the general population. It is biologically plausible that cannabis can exacerbate psychosis because psychotic disorders involve disturbances in the dopamine neurotransmitter systems, and THC increases dopamine release (Stahl, 2000).

Conclusions

The harms to health that could be caused by cannabis dependence are not as well understood as they could be. The adverse health effect that dependent users are most likely to experience is chronic bronchitis caused by regular smoking of cannabis preparations. These adverse effects will be amplified in cannabis smokers who also smoke tobacco. A birth cohort in New Zealand has found respiratory function changes in cannabis-dependent young adults that are comparable to respiratory changes attributed to low levels of daily tobacco cigarettes. There is suggestive evidence that regular cannabis smoking over a period of decades increases the risk of cancers of the upper respiratory system.

Frequent cannabis use alters brain blood flow and metabolism, but the functional significance of these findings remains obscure. Cannabis dependence is not associated with severe cognitive impairment of the type found in some alcohol-dependent persons, but there is evidence for more subtle impairments of memory, attention, and executive functions associated with long-term or heavy cannabis use. These may persist for weeks following cessation of cannabis use, and may be greater among those who commenced cannabis use during adolescence.

Some populations of cannabis-dependent persons seem at increased risk of experiencing adverse effects of their cannabis use. Foremost among these are

adults with cardiovascular disease who may precipitate myocardial infarctions by smoking cannabis; adolescents whose school performance and psychosocial development may be adversely affected and who may be at increased risk of using other illicit drugs; persons with schizophrenia and other psychoses whose illnesses may be exacerbated by continued use of cannabis; and probably persons with a family history of psychoses in whom regular cannabis use may precipitate the onset of a psychosis.

References

Ameri, A. (1999). The effects of cannabinoids on the brain. *Progress in Neurobiology*, *58*(4), 315–348.

Andreasson, S., Engstrom, A., Allebeck, P., & Rydberg, U. (1987). Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet*, *2*(8574), 1483–1486.

Anthony, J. C., Warner, L., & Kessler, R. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, *2*(3), 244–268.

Aronow, W., & Cassidy, J. (1974). Effect of marihuana and placebo marihuana smoking on angina pectoris. *New England Journal of Medicine*, *291*, 65–67.

Aronow, W., & Cassidy, J. (1975). Effect of smoking marijuana and of a high nicotine cigarette on angina pectoris. *Clinical Pharmacology and Therapeutics*, *17*, 549–554.

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T. E., *et al.* (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *British Medical Journal*, *325*(7374), 1212–1213.

Bachman, J. G., Wadsworth, K. N., O'Malley, P. M., Johnston, L. D., & Schulenberg, J. (1997). *Smoking, drinking, and drug use in young adulthood: the impacts of new freedoms and new responsibilities*. Mahwah, NJ: Lawrence Erlbaum.

Block, R. I., & Ghoneim, M. M. (1993). Effects of chronic marijuana use on human cognition. *Psychopharmacology (Berlin)*, *110*(1–2), 219–228.

Block, R. I., O'Leary, D. S., Ehrhardt, J. C., Augustinack, J. C., Ghoneim, M. M., Arndt, S., *et al.* (2000a). Effects of frequent marijuana use on brain tissue volume and composition. *Neuroreport*, *11*(3), 491–496.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Boles Ponto, L. L., Ghoneim, M. M., *et al.* (2000b). Cerebellar hypoactivity in frequent marijuana users. *Neuroreport*, *11*(4), 749–753.

Block, R. I., O'Leary, D. S., Hichwa, R. D., Augustinack, J. C., Boles Ponto, L. L., Ghoneim, M. M., *et al.* (2002). Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacology, Biochemistry and Behavior*, *72*(1–2), 237–250.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J. L. (2002). Dose-related neurocognitive effects of marijuana use. *Neurology*, *59*(9), 1337–1343.

Caplan, G. A., & Brigham, B. A. (1990). Marijuana smoking and carcinoma of the tongue: Is there an association? *Cancer, 66*(5), 1005–1006.

Chait, L. D., & Pierri, J. (1992). Effects of smoked marijuana on human performance: a critical review. In L. Murphy, & A. Bartke (Eds.), *Marijuana/cannabinoids: neurobiology and neurophysiology* (pp. 387–423). Boca Raton, FL: CRC Press.

Chesher, G. (1995). Cannabis and road safety: an outline of research studies to examine the effects of cannabis on driving skills and actual driving performance. In Parliament of Victoria Road Safety Committee (Ed.), *The effects of drugs (other than alcohol) on road safety* (pp. 67–96). Melbourne: Road Safety Committee.

Chesher, G., & Hall, W. D. (1999). Effects of cannabis on the cardiovascular and gastrointestinal systems. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 435–458). Toronto: Centre for Addiction and Mental Health.

Copeland, J., Swift, W., & Rees, V. (2001). Clinical profile of participants in a brief intervention program for cannabis use disorder. *Journal of Substance Abuse Treatment*, *20*(1), 45–52.

Degenhardt, L., Hall, W. D., & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence*, *71*(1), 37–48.

Donald, P. (1991). Marijuana and upper aerodigestive tract malignancy in young patients. In G. Nahas, & C. Latour (Eds.), *Physiopathology of illicit drugs: cannabis, cocaine, opiates* (pp. 39–54). Oxford: Pergamon.

Ehrenreich, H., Rinn, T., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L., *et al.* (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology (Berlin)*, *142*(3), 295–301.

Fergusson, D. M., Horwood, L. J., & Health, C. (2000). Cannabis use and dependence in a New Zealand birth cohort. *New Zealand Medical Journal*, *113*(1109), 156–158.

Fergusson, D. M., & Horwood, L. J. (1997). Early onset cannabis use and psychosocial adjustment in young adults. *Addiction*, *92*(3), 279–296.

Fergusson, D. M., & Horwood, L. J. (2000). Does cannabis use encourage other forms of illicit drug use? *Addiction*, *95*(4), 505–520.

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*, *97*, 1123–1135.

Fergusson, D. M., Horwood, L. J., & Beautrais, A. L. (2003a). Cannabis and educational achievement. *Addiction*, *98*(12), 1681–1692.

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. R. (2003b). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine*, *33*, 15–21.

Gerberich, S. G., Sidney, S., Braun, B. L., Tekawa, I. S., Tolan, K. K., & Queensberry, C. P. (2003). Marijuana use and injury events resulting in hospitalization. *Annals of Epidemiology*, *13*(4), 230–237.

Gottschalk, L., Aronow, W., & Prakash, R. (1977). Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological and cardiovascular functioning in angina patients. *Biological Psychiatry*, *12*(2), 255–266.

Guzman, M. (2003). Cannabinoids: potential anticancer agents. *Nature Reviews Cancer*, *3*, 745–755.

Hall, W. D. (1998). Cannabis use and psychosis. *Drug and Alcohol Review*, *17*(4), 433–444.

Hall, W. D., & Babor, T. F. (2000a). Cannabis use and public health: assessing the burden. *Addiction*, *95*(4), 485–490.

Hall, W. D., & Degenhardt, L. (2000b). Cannabis use and psychosis: a review of clinical and epidemiological evidence. *Australian and New Zealand Journal of Psychiatry*, *34*(1), 26–34.

Hall, W. D., & MacPhee, D. (2002). Cannabis use and cancer. *Addiction*, *97*(3), 243–247.

Hall, W. D., & Pacula, R. L. (2003a). *Cannabis use and dependence: public health and public policy.* Cambridge: Cambridge University Press.

Hall, W. D., & Lynskey, M. (2003b). Testing hypotheses about the relationship between the use of cannabis and the use of other illicit drugs. *Drug and Alcohol Review*, *22*(2), 125–133.

Hall, W. D., Solowij, N., & Lemon, J. (1994). *The health and psychological consequences of cannabis use*, National Drug Strategy Monograph, Vol. 25. Canberra: Australian Government Publishing Service.

Hall, W. D., Teesson, M., Lynskey, M. T., & Degenhardt, L. (1999a). The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: findings from the National Survey of Mental Health and Well-Being. *Addiction*, *94*(10), 1541–1550.

Hall, W. D., Johnston, L. D., & Donnelly, N. (1999b). Assessing the health and psychological effects of cannabis use. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 1–17). Toronto: Centre for Addiction and Mental Health.

Hall, W. D., Degenhardt, L., & Lynskey, M. T. (2001). *The health and psychological effects of cannabis use*, National Drug Strategy Monograph, Vol. 44. Canberra: Commonwealth Department of Health and Aged Care.

Han, C., McGue, M. K., & Iacono, W. G. (1999). Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses. *Addiction*, *94*(7), 981–993.

Heath, A. C. (1995). Genetic influences on alcoholism risk: a review of adoption and twin studies. *Alcohol Health and Research World*, *19*(3), 166–171.

Institute of Medicine (1999). *Marijuana and medicine: assessing the science base.* Washington, DC: National Academy Press.

Iversen, L. (2003). Cannabis and the brain. *Brain*, *126*, 1252–1270.

Jablensky, A., McGrath, J., Herrman, H., Castle, D., Gureje, O., & Evans, M. (2000). Psychotic disorders in urban areas: an overview of the Study on Low Prevalence Disorders. *Australian and New Zealand Journal of Psychiatry*, *34*(2), 221–236.

Jones, R. T. (2002). Cardiovascular system effects of marijuana. *Journal of Clinical Pharmacology*, *42*(11 Suppl.), 58S–63S.

Kendler, K. S., & Prescott, C. A. (1998). Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry*, *155*(8), 1016–1022.

Linszen, D. H., Dingemans, P. M., & Lenior, M. E. (1994). Cannabis abuse and the course of recent-onset schizophrenic disorders. *Archives of General Psychiatry*, *51*(4), 273–279.

Llewellyn, C. D., Linklater, K., Bell, J., Johnson, N. W., & Warnakulasuriya, S. (2004). An analysis of risk factors for oral cancer in young people: a case–control study. *Oral Oncology*, *40*(3), 304–313.

Loeber, R. T., & Yurgelun-Todd, D. A. (1999). Human neuroimaging of acute and chronic marijuana use: implications for frontocerebellar dysfunction. *Human Psychopharmacology – Clinical and Experimental*, *14*(5), 291–304.

Lundqvist, T., Jonsson, S., & Warkentin, S. (2001). Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicology and Teratology*, *23*(5), 437–443.

Lyketsos, C. G., Garrett, E., Liang, K. Y., & Anthony, J. C. (1999). Cannabis use and cognitive decline in persons under 65 years of age. *American Journal of Epidemiology*, *149*(9), 794–800.

Lynskey, M. T., & Hall, W. D. (2000). The effects of adolescent cannabis use on educational attainment: a review. *Addiction*, *96*(3), 433–443.

Lynskey, M. T., Fergusson, D. M., & Horwood, L. J. (1998). The origins of the correlations between tobacco, alcohol, and cannabis use during adolescence. *Journal of Child Psychology and Psychiatry*, *39*(7), 995–1005.

Lynskey, M. T., Heath, A. C., Bucholz, K. K., & Slutske, W. S. (2003). Escalation of drug use in early-onset cannabis users vs co-twin controls. *Journal of the American Medical Association*, *289*(4), 427–433.

Macleod, J., Oakes, R., Copello, A., Crome, I., Egger, M., Hickman, M., *et al.* (2004). Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. *Lancet*, *363*(9421), 1579–1588.

MacPhee, D. (1999). Effects of marijuana on cell nuclei: a review of the literature relating to the genotoxicity of cannabis. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 435–458). Toronto: Centre for Addiction and Mental Health.

Marselos, M., & Karamanakos, P. (1999). Mutagenicity, developmental toxicity and carcinogeneity of cannabis. *Addiction Biology*, *4*(1), 5–12.

Mittleman, M. A., Lewis, R. A., Maclure, M., Sherwood, J. B., & Muller, J. E. (2001). Triggering myocardial infarction by marijuana. *Circulation, 103*, 2805–2809.

Mura, P., Kintz, P., Ludes, B., Gaulier, J. M., Marquet, P., Martin-Dupont, S., *et al.* (2003). Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. *Forensic Science International, 133*(1–2), 79–85.

van Os, J., Bak, M., Hanssen, M., Bijl, R.V., de Graaf, R., *et al.* (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology, 156*(4), 319–327.

Piomelli, D. (2003). The molecular logic of endocannabinoid signalling. *Nature Reviews Neuroscience, 4*(11), 873–884.

Pope, H. G., & Yurgelun-Todd, D. (1996). The residual cognitive effects of heavy marijuana use in college students. *Journal of the American Medical Association, 275*(7), 521–527.

Pope, H. G., Gruber, A. J., & Yurgelun-Todd, D. (1995). The residual neuropsychological effects of cannabis: the current status of research. *Drug and Alcohol Dependence, 38*(1), 25–34.

Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58*(10), 909–915.

Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2002). Cognitive measures in long-term cannabis users. *Journal of Clinical Pharmacology, 42*(11 Suppl.), 41S–47S.

Porrino, L. J., Whitlow, C. T., Lamborn, C., Laurienti, P. J., Livengood, L. B., & Liguori, A. (2004). Impaired performance on a decision-making task by heavy marijuana users: an fMRI study. In *2004 Symposium on the Cannabinoids* (p. 239). Burlington, VT: International Cannabinoid Research Society.

Ramaekers, J. G., Berghaus, G., van Laar, M., & Drummer, O. H. (2004). Dose related risk of motor vehicle crashes after cannabis use. *Drug and Alcohol Dependence, 73*(2), 109–119.

Rosenblatt, K. A., Daling, J. R., Chen, C., Sherman, K. J., & Schwartz, S. M. (2004). Marijuana use and risk of oral squamous cell carcinoma. *Cancer Research, 64*(11), 4049–4054.

Sidney, S. (2002). Cardiovascular consequences of marijuana use. *Journal of Clinical Pharmacology, 42*(11 Suppl.), 64S–70S.

Sidney, S., Quesenberry Jr., C. P., Friedman, G. D., & Tekawa, I. S. (1997). Marijuana use and cancer incidence (California, United States). *Cancer Causes and Control, 8*(5), 722–728.

Smiley, A. (1999). Marijuana: on road and driving simulator studies. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 171–191). Toronto: Centre for Addiction and Mental Health.

Smith, A. M., Fried, P. A., Hogan, M. J., & Cameron, I. (2004). Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicology and Teratology, 26*(4), 533–542.

Solowij, N. (1998). *Cannabis and cognitive functioning.* Cambridge, UK: Cambridge University Press.

Solowij, N. (1999). Long-term effects of cannabis on the central nervous system. I. Brain function and neurotoxicity. II. Cognitive functioning. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 195–265). Toronto: Centre for Addiction and Mental Health.

Solowij, N. (2002). Marijuana and cognitive function. In E. S. Onaivi (Ed.), *Biology of marijuana: from gene to behaviour* (pp. 308–332). London: Taylor and Francis.

Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., *et al.* (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. *Journal of the American Medical Association, 287*(9), 1123–1131.

Solowij, N., Respondek, C., & Ward, P. (2004). Functional magnetic resonance imaging indices of memory function in long-term cannabis users. In *2004 Symposium on the Cannabinoids* (p. 89). Burlington, VT: International Cannabinoid Research Society.

Stahl, S. M. (2000). *Essential psychopharmacology: neuroscientific basis and practical applications* (2nd ed.). Cambridge, UK: Cambridge University Press.

Swift, W., Hall, W. D., & Copeland, J. (1998a). Characteristics of long-term cannabis users in Sydney, Australia. *European Addiction Research, 4*(4), 190–197.

Swift, W., Hall, W. D., Didcott, P., & Reilly, D. (1998b). Patterns and correlates of cannabis dependence among long-term users in an Australian rural area. *Addiction, 93*(8), 1149–1160.

Swift, W., Hall, W. D., & Teesson, C. (2001). Characteristics of DSM-IV and ICD-10 cannabis dependence among Australian adults: results from the National Survey of Mental Health and Well-being. *Drug and Alcohol Dependence, 63*(2), 147–153.

Tashkin, D. P. (1999). Effects of cannabis on the respiratory system. In H. Kalant, W. Corrigall, W. D. Hall, & R. Smart (Eds.), *The health effects of cannabis* (pp. 311–345). Toronto: Centre for Addiction and Mental Health.

Taylor, I. F. (1988). Marijuana as a potential respiratory tract carcinogen: a retrospective analysis of a community hospital population. *Southern Medical Journal, 81*(10), 1213–1216.

Taylor, D. R., Poulton, R., Moffitt, T. E., Ramankutty, P., & Sears, M. R. (2000). The respiratory effects of cannabis dependence in young adults. *Addiction, 95*(11), 1669–1677.

Taylor, D. R., Fergusson, D. M., Milne, B. J., Horwood, L. J., Moffitt, T. E., Sears, M. R., *et al.* (2002). A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction, 97*(8), 1055–1061.

True, W. R., Heath, A. C., Scherrer, J. F., Xian, H., Lin, N., Eisen, S. A., *et al.* (1999). Interrelationship of genetic and environmental influences on conduct disorder and

alcohol and marijuana dependence symptoms. *American Journal of Medical Genetics*, *88*(4), 391–397.

Verdoux, H., Gindre, C., Sorbara, F., Tournier, M., & Swendsen, J. (2002). Cannabis use and the expression of psychosis vulnerability in daily life. *European Psychiatry*, *17*(Suppl.), 180S–190S.

Wilson, W., Mathew, R., Turkington, T., Hawk, T., Coleman, R. E., & Provenzale, J. (2000). Brain morphological changes and early marijuana use: a magnetic resonance and positron emission tomography study. *Journal of Addictive Diseases*, *19*(1), 1–22.

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self-reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *British Medical Journal*, *325*(7374), 1199–1201.

Zhang, Z. F., Morgenstern, H., Spitz, M. R., Tashkin, D. P., Yu, G. P., Marshall, J. R., *et al.* (1999). Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiology Biomarkers and Prevention*, *8*(12), 1071–1078.

Part II

Interventions with Cannabis-Dependent Adults