



Review

The adverse health effects of cannabis use: What are they, and what are their implications for policy?

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ABSTRACT

Background: The adverse health effects of cannabis are a source of contention in debates about policies towards the drug. **Methods:** This paper provides a review of epidemiological evidence on the major adverse health effects of cannabis use and considers its implications for policy. **Results:** The evidence strongly suggests that cannabis can adversely affect some users, especially adolescents who initiate use early and young adults who become regular users. These adverse effects probably include increased risks of: motor vehicle crashes, the development of cannabis dependence, impaired respiratory function, cardiovascular disease, psychotic symptoms, and adverse outcomes of adolescent development, namely, poorer educational outcomes and an increased likelihood of using other illicit drugs. **Conclusions:** Politically, evidence of adverse health effects favours the status quo in developed countries like Australia where cannabis policy has been framed by the media as a choice between two views: (1) either cannabis use is largely harmless to most users and so we should legalize, or at the very least decriminalize its use; or (2) it harms some of its users so we should continue to prohibit its use.

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Cannabis is a relatively “new” recreational drug that has only been widely used by adolescents and young adults in the USA since the late 1970s and in other developed countries since the late 1980s and the early 1990s (Hall & Pacula, 2003). Rising use has heightened community concern about the impact of cannabis use on the health and psychological development of young people because of observations that regular cannabis users are more likely to use other illicit drugs, perform poorly in schools, and report psychotic symptoms, depression and poorer mental health than their peers (Hall, 2006). These concerns have been heightened by media reports that the potency of cannabis products has substantially increased (Hall & Swift, 2000).

This paper selectively reviews evidence on the adverse health effects of cannabis that are likely to be of public health concern and discusses the implications of these effects for the policy debate about how we should respond to the use of cannabis by young people. More comprehensive reviews are provided by Hall and Pacula (2003) and Room, Fischer, Hall, Lenton, and Reuter (2008).

Acute adverse health effects of cannabis

The most common adverse unpleasant effects of occasional cannabis use are anxiety and panic reactions (Hall & Pacula, 2003;

Kalant, 2004). These may be reported by naïve users among whom they are a common reason for discontinuing use (Hall & Pacula, 2003). The acute toxicity of cannabinoids is very low because they do not produce respiratory depression like the opioids (Gable, 2004; Kalant, 2004). The estimated fatal dose in humans is 15 g, many times greater than the dose that heavy users could consume in a day (Gable, 2004).

Accidental injury

The acute effect of greatest public health concern is that cannabis intoxicated drivers may cause motor vehicle crashes (Hall & Pacula, 2003). In laboratory studies cannabis produces decrements in cognitive and behavioural performance that may affect accident risk (Ramaekers, Berghaus, van Laar, & Drummer, 2004; Robbe, 1994). These increase with THC dose and are larger in tasks requiring sustained attention (Chait & Pierri, 1992; Solowij, 1998).

In surveys drivers who report using cannabis are twice as likely to report being involved in accidents than drivers who do not (e.g. Asbridge, Poulin, & Donato, 2005; Hingson, Heeren, Mangione, Morelock, & Mucatel, 1982; Smart & Fejer, 1976). Studies of the effects of cannabis upon on-road driving performance have found modest impairments because cannabis intoxicated drivers drive more slowly and take fewer risks than alcohol-intoxicated ones (Smiley, 1999). More recent studies of on-road driving using doses closer to typical recreational ones (e.g. Robbe, 1994) have

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found small but consistent decrements in driving performance (Ramaekers et al., 2004).

Cannabis is the illicit drug most often detected in drivers who have been injured or killed in motor vehicle crashes (see Kelly, Darke, & Ross, 2004 for a review). For a number of reasons it has been uncertain whether cannabis played a causal role in these accidents (Hall, Degenhardt, & Lynskey, 2001). First, most early studies measured inactive cannabinoid metabolites which did not indicate that the driver was intoxicated at the time of the accident (see Bates & Blakely, 1999; Hall et al., 2001; Kelly et al., 2004 for reviews). Second, many drivers in these studies who had cannabinoids in their blood also had high blood alcohol levels (Bates & Blakely, 1999; Hall et al., 2001).

Better controlled epidemiological studies have since provided stronger evidence that cannabis intoxicated drivers have an increased risk of motor vehicle crashes (Grotenhermen et al., 2007). Gerberich et al. (2003), for example, assessed the relationship between self-reported cannabis use and hospitalisation for accidental injury in 64,657 patients in a Health Maintenance Organization. Cannabis users had higher rates of injury from all causes, including self-inflicted injury, motor vehicle accidents and assaults than non-users (RR = 1.96) after statistical adjustment. Laumon, Gadegebeku, Martin, and Biecheler (2005) found increased culpability for drivers with THC in their blood at levels of greater than 1 ng/ml (OR = 2.87) in a study of 6766 culpable drivers and 3006 nonculpable controls in France. They estimated that 2.5% of fatal accidents in France could be attributed to cannabis compared with 29% to alcohol in drivers with a BAC of greater than 0.05%.

A convergence of evidence strongly suggests that cannabis use before driving increases the risk of motor vehicle crashes 2–3 times (Ramaekers et al., 2004). The relative risk of accidents in intoxicated cannabis users is more modest than that of alcohol (1.3–3 vs. 6–15 for alcohol). The attributable risk of cannabis to car crashes is also much smaller than that of alcohol (2.5% vs. 29%), reflecting the lower crash risks in cannabis impaired drivers and the lower prevalence of cannabis impaired drivers.

The adverse health effects of chronic cannabis use

“Chronic” cannabis use includes regular (especially daily or near daily) use over periods of years. A major problem in interpreting epidemiological studies of chronic cannabis use is that it is also correlated with other drug use, which is known to adversely affect health (e.g. alcohol and tobacco use). This makes it difficult to confidently attribute some of the adverse health effects found in cannabis users to their cannabis use (Hall, 1999). In the case of adverse psychosocial outcomes (e.g. poor educational attainment and mental disorders) an additional interpretive problem is that heavy cannabis users differ from non-users before using cannabis in ways that predict increased risks of these outcomes (Macleod et al., 2004). Statistical control of confounding has been the most widely used approach to deal with these interpretive problems. So far much less use has been made of policy experiments (e.g. evaluating the effects of school-based prevention programs on adolescent mental health or the use of other illicit drugs).

Cannabis dependence

Cannabis dependence is the most common type of drug dependence after alcohol and tobacco in mental health surveys in developed societies (Anthony & Helzer, 1991; Kessler et al., 1994; Hall, Teesson, Lynskey, & Degenhardt, 1999). Around 2% of the adult population met criteria for this disorder in the past year (Swift, Hall, & Teesson, 2001), with a lifetime prevalence of 4% in the USA (Anthony, Warner, & Kessler, 1994). The risk of cannabis dependence is around 9% among persons who have ever used the drug

(Anthony et al., 1994; Anthony, 2006). This increases to one in six among those who initiate cannabis use during adolescence (Anthony, 2006) and to between one in three and one in two among daily users (Hall & Pacula, 2003). Those at highest risk of developing dependence are those who initiate early and have a history of: poor academic achievement, deviant behaviour in childhood and adolescence, nonconformity and rebelliousness, poor parental relationships, and a parental history of drug and alcohol problems (Anthony, 2006; Coffey, Carlin, Lynskey, Li, & Patton, 2003).

Animals and humans develop tolerance to many of the behavioural and physiological effects of THC (Adams & Martin, 1996; Compton, Dewey, & Martin, 1990; Maldonado, 2002). The cannabinoid antagonist SR 141716A precipitates a withdrawal syndrome in rats, mice and dogs (e.g. Aceto, Scates, Lowe, & Martin, 1996; Cook, Lowe, & Martin, 1998; Lichtman et al., 1998; Selley, Lichtman, & Martin, 2003; Tsou, Patrick, & Walder, 1995) that is reversed by THC (Lichtman, Fisher, & Martin, 2001).

Cannabis withdrawal symptoms have been observed in humans (Budney & Hughes, 2006) who have been abruptly withdrawn after 20 days of high dose THC (Jones, Benowitz, & Herning, 1976) and in long-term cannabis users (Kouri & Pope, 2000). The typical symptoms are decreased mood and appetite and increased irritability, anxiety, and depression (Kouri & Pope, 2000). These symptoms appear within 24 h of cessation and are most pronounced for the first 10 days. Dependent cannabis users seeking help to stop often report withdrawal symptoms, including anxiety, insomnia, appetite disturbance and depression (Budney, Novy, & Hughes, 1999; Budney, Hughes, Moore, & Vandrey, 2004; Budney & Hughes, 2006; Copeland, Swift, & Rees, 2001; Stephens, Roffman, & Simpson, 1994; Swift, Hall, & Copeland, 1998; Wiesbeck et al., 1996). They also report using cannabis to relieve withdrawal symptoms (Budney & Hughes, 2006).

Over the past two decades, increasing numbers of cannabis users have sought help from drug treatment services in the USA, Europe, and Australia because of difficulties in stopping their cannabis use (AIHW, 2006; Dennis, Babor, Roebuck, & Donaldson, 2002; EMCDDA, 2003; SAMHSA, 2004; Shand & Mattick, 2001). Some have argued that in the US this is the result of increased diversion of cannabis users into treatment by the courts (Zimmer & Morgan, 1997). This has not been true in the Netherlands where between 1994 and 2001 there was an increase in treatment seeking by cannabis users, despite the fact that the personal use and small scale retail sales were decriminalised over a decade earlier (Dutch National Alcohol & Drug Information System, 2004).

The respiratory risks of cannabis smoking

Over the past two decades studies in the USA (Tashkin, Baldwin, Sarafian, Dubinett, & Roth, 2002) and New Zealand (Aldington et al., 2007; Taylor, Poulton, Moffitt, Ramankutty, & Sears, 2000; Taylor et al., 2002), have shown that regular cannabis smokers report more symptoms of chronic bronchitis than non-smokers (see Tashkin et al., 2002; Tetrault et al., 2007 for reviews). The immunological competence of their respiratory systems is also impaired, increasing rates of respiratory infections and pneumonia, and their use of health services for these infections (Tashkin et al., 2002).

The effects of long-term cannabis smoking on respiratory function are less clear (Tashkin et al., 2002; Tetrault et al., 2007). A longitudinal study (Taylor et al., 2000, 2002) of respiratory function in 1037 New Zealand youths followed from birth until the ages of 21 (Taylor et al., 2000) and 26 (Taylor et al., 2002) found that impaired respiratory function in cannabis dependent subjects but this finding has not been replicated in longer follow up studies of regular smokers (Tashkin et al., 2002).

There is no evidence to date that chronic cannabis smoking increases the risk of emphysema (Tashkin, 2001). Follow up studies

of regular users over 8 years failed to find increased rates of emphysema in cannabis-only smokers (Tashkin, 2001). The same result has recently been reported in a similarly recruited group of heavy cannabis-only smokers in New Zealand (Aldington et al., 2007).

Respiratory and other cancers

There are good reasons for believing that cannabis can cause cancers of the lung and the aerodigestive tract (Hall & MacPhee, 2002; Hashibe et al., 2005). Cannabis smoke contains many of the same carcinogens as tobacco smoke which causes respiratory cancer (Hashibe et al., 2005; Marselos & Karamanakos, 1999). Some of these carcinogens occur at higher levels in cannabis than tobacco smoke (Moir et al., 2008). Cannabis smoke is mutagenic in the Ames test and causes cancers in the mouse skin test (MacPhee, 1999; Marselos & Karamanakos, 1999). Cannabis smokers inhale more deeply than tobacco smokers, retaining more tar and particulate matter (Hashibe et al., 2005; Tashkin, 1999), and chronic cannabis smokers show many of the pathological changes in lung cells that precede the development of cancer in tobacco smokers (Tashkin, 1999).

Epidemiological studies of upper respiratory tract cancers in cannabis users have produced mixed results. Sidney, Quesenberry, Friedman, and Tekawa (1997) studied cancer incidence in an 8.6 year follow up of 64,855 members of the Kaiser Permanente Medical Care Program. There was no increased risk of respiratory cancer at follow up among those who had ever used cannabis and current cannabis users. Males who had smoked cannabis had an increased risk of prostate cancer ($RR = 3.1$), and so did current cannabis smokers ($RR = 4.7$). Zhang et al. (1999), by contrast, found an increased risk of squamous cell carcinoma of the head and neck among cannabis users in a case–control study of 173 persons with this cancer and 176 controls. There was an odds ratio of 2 for cannabis smoking after adjusting for cigarette smoking, alcohol use, and other risk factors. Two other case–control studies of oral squamous cell carcinoma, however, have failed to find any association between cannabis use and oral cancers. Llewellyn, Linklater, Bell, Johnson, and Warnakulasuriya (2004) failed to find any association between self-reported cannabis use and oral cancers in a study of 116 cases and 207 age and sex matched controls. Rosenblatt et al. also reported a null finding in a community-based study of 407 cases and 615 controls aged 18–65 years in Washington State (Rosenblatt, Daling, Chen, Sherman, & Schwartz, 2004).

Case–control studies of cannabis smoking and lung cancer have produced more associations but their interpretation is uncertain (Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). A Tunisian case–control study of 110 cases of hospital diagnosed lung cancer and 110 community controls found an association with cannabis use ($OR = 8.2$) that persisted after adjustment for cigarette smoking, water pipe and snuff use (Hsairi et al., 1993; reported by Hashibe et al., 2005). A Moroccan case–control study of 118 cases and 235 control subjects also found an increased risk of lung cancer ($OR = 5.64$) among users those who smoked a combination of cannabis flowers and tobacco but a more marginal relationship for those who only smoked cannabis (Hashibe et al., 2005). A New Zealand case–control study of lung cancer in 79 adults under the age of 55 years and 324 community controls (Aldington et al., 2008) reported a dose–response relationship between lung cancer risks and frequency of cannabis use. Among the highest third of cannabis users by frequency of use, there was a 5.7 times higher risk of lung cancer (95% CI: 1.5, 21.6). A recent US case–control study (Hashibe et al., 2006) found a crude association between cannabis smoking and the risk of head, neck and lung cancer but the associations were no longer significant after controlling for tobacco smoking.

The risks of oral and respiratory cancers among cannabis smokers remain uncertain (Hashibe et al., 2005; Mehra et al., 2006). Any risk of oral cancer is probably small compared to that of tobacco

smoking, given the small relative risk in the only positive study (Rosenblatt et al., 2004). The findings from the case–control studies of lung cancer are more suggestive of increased risk but the measures of cannabis use in these studies have been relatively crude and it is unclear how well these studies have controlled for the effects of tobacco smoking. Larger cohort and better designed case–control studies of tobacco-related cancers are needed to clarify the relationship between cannabis smoking and the risks of these cancers (Hall & MacPhee, 2002; Hashibe et al., 2005).

Cardiovascular effects of cannabis smoking

In humans and animals cannabis and THC produce dose-related increases in heart rate (Chesher & Hall, 1999; Jones, 2002). The hearts of healthy young adults are only mildly stressed and tolerance develops quickly (Institute of Medicine, 1999; Jones, 2002; Sidney, 2002). There is more concern about these effects in older adults with ischaemic heart disease, hypertension, and cerebrovascular disease (Jones, 2002; Sidney, 2002). A case–crossover study by Mittleman, Lewis, Maclure, Sherwood, and Muller (2001) of 3882 patients who had had a myocardial infarction suggested that cannabis use increased the risk of a myocardial infarction 4.8 times in the hour after use. These findings are consistent with laboratory studies showing that smoking cannabis adversely affects patients with heart disease (Aronow & Cassidy, 1974, 1975; Gottschalk, Aronow, & Prakash, 1977).

The psychosocial consequences of adolescent cannabis use

Educational outcomes

Surveys typically find associations between cannabis use and poor educational attainment among school children and youth (e.g. Lifrak, McKay, Rostain, Alterman, & Obrien, 1997; Resnick et al., 1997; see Lynskey & Hall, 2000 for a review) and rates of cannabis use are higher among young people who no longer attend school or who had high rates of absenteeism (Fergusson, Lynskey, & Horwood, 1996; Lynskey, White, Hill, Letcher, & Hall, 1999). One explanation of these associations is that cannabis use is a contributory cause of poor school performance (e.g. Kandel, Davies, Karus, & Yamaguchi, 1986). A second possibility is that heavy cannabis use is a consequence of poor educational attainment (Duncan, Duncan, Biglan, & Ary, 1998; Hawkins, Catalano, & Miller, 1992). The first and second hypotheses could both be true (Krohn, Lizotte, & Perez, 1997) if, for example, poor school performance increased cannabis use which in turn further impaired school performance. A third hypothesis is that cannabis use and poor educational attainment are the result of common factors that increase the risk of both early cannabis use and poor educational performance (Donovan & Jessor, 1985; Jessor & Jessor, 1977). This hypothesis is supported by the overlap between risk factors for early cannabis use and poor educational performance (see Hawkins et al., 1992).

These competing explanations can potentially be distinguished by prospective studies of young people who are assessed over time on their cannabis use, educational attainment and potentially confounding factors, such as family and social circumstances, personality characteristics and delinquency (Lynskey & Hall, 2000). These studies enable researchers 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 have a history of poor school performance and other characteristics before they used cannabis?

Such studies (e.g. Fergusson et al., 1996) have typically found a relationship between cannabis use before the age of 15 years and early school leaving that has persisted after statistical adjustment for differences between early cannabis users and their peers. (e.g.

Duncan et al., 1998; Ellickson, Bui, Bell, & McGuigan, 1998; Krohn et al., 1997; Tanner, Davies, & O'Grady, 1999). The most plausible hypothesis seems to be that the impaired educational performance in adolescent cannabis users is attributable to a higher pre-existing risk of these outcomes and a combination of the effects of acute intoxication upon cognitive performance, affiliation with peers who reject school, and a desire to make an early transition to adulthood (Lynskey & Hall, 2000).

Other illicit drug use

Surveys of adolescent drug use in the United States over the past 30 years have consistently shown three relationships between cannabis and the use of heroin and cocaine (Kandel, 2002). First, almost all of those who tried cocaine and heroin first used alcohol, tobacco and cannabis (Kandel, 2002). Second, regular cannabis users were most likely to later use heroin and cocaine (Kandel, 1984). Third, the earlier the age at which cannabis was first used, the more likely a user was to use heroin and cocaine (Donovan & Jessor, 1983; Kandel, 1988, 2002). These relationships have been confirmed in longitudinal studies of drug use in New Zealand (Fergusson & Horwood, 1997, 1999, 2000; McGee & Feehan, 1993).

Three types of explanation have been offered for these patterns of drug involvement. The first is that because cannabis and other illicit drugs are supplied by the same black market, cannabis users have more opportunities to use other illicit drugs than non-cannabis users (Cohen, 1976). The second hypothesis is that those who are early cannabis users are more likely to use other illicit drugs for reasons unrelated to their cannabis use (Morral, McCaffrey, & Paddock, 2002). The third hypothesis is that the pharmacological effects of cannabis increase the propensity to use other illicit drugs (Murray, Morrison, Henquet, & Di Forti, 2007).

Social environment and drug availability do play a role. Young people in the USA who have used cannabis report more opportunities to use cocaine at an earlier age (Wagner & Anthony, 2002). In New Zealand, however, self-reported affiliation with drug using peers only partially explains the relationship between cannabis and other illicit drug use (Fergusson & Horwood, 2000).

There is also evidence that socially deviant young people who have a predilection to use a variety of drugs including alcohol, cannabis, cocaine and heroin are more likely to be recruited to early cannabis use (Fergusson & Horwood, 2000). The selective recruitment hypothesis is supported by correlations between dropping out of high school, early premarital sexual experience, delinquency, and early alcohol and illicit drug use (Jessor & Jessor, 1977; Osgood, Johnston, O'Malley, & Bachman, 1988), all of which are more likely in regular cannabis users than their non-using peers (Hawkins et al., 1992; Kandel & Davies, 1992; McGee & Feehan, 1993). The selective recruitment hypothesis has also been supported by a simulation study (Morral et al., 2002) which showed that this model reproduced all the relationships between cannabis and other illicit drug use described above.

The selective recruitment hypothesis has been tested in longitudinal studies by assessing whether cannabis users are more likely to report heroin and cocaine use after statistically controlling for pre-existing differences between them and non-users (e.g. Fergusson & Horwood, 2000; Fergusson, Horwood, & Swain-Campbell, 2002; Fergusson, Horwood, & Ridder, 2005; Fergusson, Boden, & Horwood, 2006; Kandel et al., 1986). Generally, adjustment for these pre-existing differences weakens but does not eliminate the strong relationships between early and regular cannabis use of other illicit drugs (see Hall & Lynskey, 2005 for a review).

Twin studies have tested another explanation of the association between cannabis and other illicit drug use: that it is due to a shared genetic vulnerability to use cannabis and other illicit drugs (Han, McGue, & Iacono, 1999; True et al., 1999). Lynskey, Heath, Bucholz,

and Slutske (2003) tested this hypothesis by assessing the relationship between cannabis and other illicit drug use in 136 monozygotic and 175 dizygotic twin pairs in which one twin had, and the other twin had not, used cannabis before the age of 17 years. Lynskey et al. found that the twin who had used cannabis was more likely to have used sedatives, hallucinogens, stimulants and opioids than their co-twin who had not. These relationships persisted after controlling for other non-shared environmental factors that predicted an increased risk of developing drug use or dependence.

Animal studies suggest a number of ways in which the pharmacological effects of cannabis use could predispose cannabis users to use other illicit drugs. First, cannabis, cocaine, heroin and nicotine all act on the same brain "reward centre" in the nucleus accumbens (Gardner, 1999). Second, the cannabinoid and opioid systems in the brain interact with each other (Manzanares et al., 1999; Tanda, Pontieri, & Di Chiara, 1997). Third, mutant mice in which the cannabinoid receptor has been "knocked out" do not find opioids rewarding (Ledent et al., 1999).

Animal studies also potentially provide direct tests of whether these neural mechanisms may explain the relationship between cannabis and other illicit drug use in humans. Specifically, they can assess whether self-administration of cannabinoids "primes" animals to self-administer other illicit drugs (Zimmer & Morgan, 1997). Two studies in rats (Cadoni, Pisanu, Solinas, Acquas, & Di Chiara, 2001; Lamarque, Taghzouti, & Simon, 2001), for example, have provided some evidence for cross-sensitivity between cannabinoids and opioids (Lamarque et al., 2001). Their relevance to adolescent cannabis use is uncertain, however, because these effects were produced by injecting large doses of cannabinoids (Lynskey, 2002).

Cannabis use is more strongly associated with other illicit drug use than alcohol or tobacco use, and the earliest and most frequent cannabis users are the most likely to use other illicit drugs. Animal studies provide some biological plausibility for a causal relationship between cannabis and other types of illicit drug use. Nonetheless, it has been difficult to exclude the hypothesis that the pattern of use reflects the common characteristics of those who use cannabis and other drugs (Macleod et al., 2004). Well controlled longitudinal studies suggest that selective recruitment to cannabis use does not wholly explain the association between cannabis use and the use of other illicit drugs. This is supported by a discordant twin study which suggests that shared genes and environment do not wholly explain the association.

Cannabis use and psychosis

Cannabis use and psychotic symptoms are associated in general population surveys (Degenhardt & Hall, 2001; Stefanis et al., 2004; Thomas, 1996; Tien & Anthony, 1990) and the relationship persists after adjusting for confounders (e.g. Degenhardt & Hall, 2001). The best evidence that these associations may be causal comes from longitudinal studies.

One of the earliest prospective studies of cannabis use and schizophrenia was a 15-year follow up of 50,465 Swedish conscripts. It 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 (Andreasson, Engstrom, Allebeck, & Rydberg, 1987). The risk increased with the frequency of cannabis use and remained significant after statistical adjustment for confounding variables. Those who had used cannabis 10 or more times by age 18 were 2.3 times more likely to be diagnosed with schizophrenia than those who had not. Zammit, Allebeck, Andreasson, Lundberg, and Lewis (2002) reported a 27-year follow up of the Swedish cohort. They also found a dose-response relationship between frequency of cannabis use at age 18 and risk of schizophrenia during the follow up. They also demonstrated that the relationship persisted after statistically controlling for the effects of other drug use and other

potential confounding factors. They estimated that 13% of cases of schizophrenia could be averted if all cannabis use were prevented. This estimate may be positively biased if there is residual confounding in measurement of the association.

Zammit et al.'s findings have been supported by other longitudinal studies. A 3-year longitudinal study of the relationship between self-reported cannabis use and psychosis in a sample of 4848 people in the Netherlands (van Os et al., 2002) found a dose–response relationship between cannabis use at baseline and psychotic symptoms during the follow up period that persisted after statistically controlling for the effects of other drug use. Henquet et al. (2004) reported a 4-year follow up of a cohort of 2437 adolescents and young adults between 1995 and 1999 in Munich which found a dose–response relationship between self-reported cannabis use at baseline and the likelihood of reporting psychotic symptoms at follow up. Arseneault et al. (2002) found a relationship between cannabis use by age 15 and an increased risk of psychotic symptoms by age 26 in a New Zealand birth cohort. Fergusson, Horwood and Swain-Campbell (2003) reported similar findings from a longitudinal study of the Christchurch birth cohort. Cannabis dependence at age 18 predicted an increased risk of psychotic symptoms at age 21 years (RR of 2.3) which was reduced but still significant after adjustment for potential confounders (RR of 1.8).

Moore et al. (2007) conducted a meta-analysis of these longitudinal studies that reported an odds ratio of 1.4 [95% CI: 1.20, 1.65] of psychotic disorders among those who had ever used cannabis. There was also a dose–response relationship between frequency of cannabis use and the risk of developing psychotic symptoms or a psychotic disorder. Reverse causation was controlled in the majority of these studies by either excluding cases reporting psychotic symptoms at baseline or by statistically adjusting for pre-existing psychotic symptoms. The common causal hypothesis was harder to exclude in all studies because the association between cannabis use and psychosis was attenuated after statistical adjustment for some potential confounders and no study assessed all major potential confounders.

Has the incidence of schizophrenia, particularly early-onset acute cases, changed over the period when there have been very substantial increases in cannabis use among young adults in Australia and North America? A study modelling trends in the incidence of psychoses in Australia did not find clear evidence of any increase in psychosis incidence following steep increases in cannabis use during the 1980s (Degenhardt, Hall, & Lynskey, 2003). A similar study in Britain (Hickman, Vickerman, Macleod, Kirkbride, & Jones, 2007) suggested that it may be too early to detect any effect that cannabis use has on the incidence of psychoses in the UK because its use only increased during the 1990s. Other recent British (Boydell et al., 2006) and Swiss studies (Ajdacic-Gross et al., 2007) have reported suggestive increases in the incidence of psychoses among males in recent birth cohorts.

A study that found an interaction between cannabis use and a common polymorphism in the COMT Val¹⁵⁸Met allele has suggested a biological basis for the relationship between cannabis use and psychosis (Caspi et al., 2005). Alterations in catecholamine, particularly dopamine, metabolism have been documented in persons with schizophrenia (Bildner, Volavka, Lachman, & Grace, 2004) and the COMT functional polymorphism is very important for the metabolism of dopamine (Mannisto & Kaakkola, 2006). There is also some experimental support for a direct effect of cannabis on psychotic symptoms from a provocation study by D'Souza et al. (D'Souza, Cho, Perry, & Krystal, 2004; D'Souza et al., 2005; D'Souza, 2007) in which intravenous THC given under double-blind placebo controlled conditions produced dose-dependent increases in positive and negative psychotic symptoms in patients with schizophrenia in remission.

The effects of increased THC in cannabis products

Regular monitoring of cannabis products in the USA indicates that THC content has increased from less than 2% in 1980 to 4.5% in 1997 (ElSohly et al., 2000) and more recently to 8.5% (ONDCP, 2007). THC content also increased in the Netherlands between 2000 and 2005 (Pijlman, Rigter, Hoek, Goldschmidt, & Niesink, 2005). It may also have increased in other European countries (Murray et al., 2007) although it is uncertain by how much in the absence of time series data on THC in representative samples of cannabis products (EMCDDA, 2004; McLaren, Swift, Dillon, & Allsop, 2008).

The net effect of any increase in the potency of cannabis products on users' health will depend considerably on the extent to which users are able to offset the effects of increased THC by being able to, and choosing to, titrate the dose of THC that they obtain from smoking cannabis (Hall & Swift, 2000). Among naive users, higher THC content may increase the likelihood of adverse psychological effects, such as anxiety, depression and psychotic symptoms. These may discourage first time users from continuing to use the drug. Among continuing users, increased potency might increase the risk of dependence (Hall & Pacula, 2003). If regular users fail to fully compensate for increased potency, this would increase the risk of vulnerable users experiencing psychotic symptoms. Any adverse effects of cannabis smoking on respiratory and cardiovascular systems may be reduced in regular users if they are able to titrate to a desired dose of THC. Increased potency could also plausibly increase the risk of road traffic crashes if users drive while intoxicated (Hall & Pacula, 2003).

The adverse health effects of cannabis and other drugs

The major acute adverse effects of cannabis use are anxiety and panic and an increased risk of accident if a person drives a motor vehicle while intoxicated with cannabis. The chronic health effects are less certain because the evidence is from observational studies that often have limited ability to adequately control for major sources of confounding or to rule out reverse causation. This is especially true in the case of the putative effects of cannabis use on adolescent development (Macleod et al., 2004). Accepting these limitations on the evidence, the most *probable* adverse effects of chronic use are: a cannabis dependence syndrome; chronic bronchitis and impaired respiratory function; respiratory cancers; cardiovascular disease and psychotic disorders in heavy users, especially those with a personal or family history of such symptoms. Among the most *probable* adverse psychosocial effects are impaired educational attainment in adolescents and an increased likelihood of using other illicit drugs, although these remain contested because of difficulties in ruling out residual confounding (Macleod et al., 2004).

Cannabis, *on current patterns of use*, probably has a small to moderate adverse public health impact by comparison with alcohol, tobacco, heroin and methamphetamine (Hall, 1995; Hall, Room, & Bondy, 1999; Hall & Pacula, 2003). With the exception of motor vehicle accidents, most of the probable harms that arise from cannabis use are experienced by the minority who become regular users of the drug (Hall & Pacula, 2003).

Adverse health effects and cannabis policy

The adverse health effects of cannabis have major policy resonance because in many developed countries like Australia, Canada, the United Kingdom and the USA the debate about cannabis policy has been simplified in the popular media to a choice of two options: (1) we should legalise cannabis, or at the very least decriminalise its use, because its use is harmless; or (2) we should continue to

prohibit cannabis use because it is harmful to users (Hall, 1997, 2007).

Given this simplification, an honest appraisal of the adverse health effects of cannabis use complicates the cannabis policy debate. Supporters of cannabis prohibition are troubled by the fact that the adverse health consequences are not manifestly more serious than those of alcohol and tobacco while advocates of reform are often reluctant to concede that cannabis use has any adverse effects (e.g. Zimmer & Morgan, 1997) for fear of giving up the most compelling argument for reform, namely, that cannabis use is harmless.

As argued in more detail elsewhere (Hall, 2007), we should reject this policy simplification because it does not follow that cannabis use should be prohibited simply because it harms some users. Those who support cannabis prohibition also need to show that criminal penalties are the best way to discourage cannabis use and decrease the harms that it causes, and that the social costs of using the criminal law to deter people from using cannabis are worth bearing (Hall & Pacula, 2003; MacCoun & Reuter, 2001; Manski, Pepper, & Petrie, 2001).

Cannabis policy: a choice of evils

Ideally, the formulation of cannabis policy requires a societal process for weighing the costs and benefits of cannabis use against the costs and benefits of prohibiting its use (Kleiman, 1992). Research evidence cannot be decisive in policy debates when there are strong differences of opinion between key stakeholders about policy goals and the interpretation of evidence (Sindall, 2003; Weiss, 1983). Debates over the ends of policies are inherently political and in democratic societies they are ideally resolved by a deliberative political process that takes evidence into account when negotiating policy compromises that are the most acceptable to the most people (or the least objectionable to the fewest) (Sindall, 2003; Weiss, 1983).

The role that evidence can play in formulating cannabis policies in Australia and many English-speaking democracies has been limited by a number of factors. First, the policy options are limited by international drug control treaties that prohibit the legalisation of cannabis production, sale and use (McDonald, Moore, Norberry, Wardlaw, & Ballenden, 1994). These treaties are strongly supported by the international community, the USA (Brereton, 2000), and often by the public. Second, the media framing of cannabis policy outlined above encourages the selective appeal to evidence on the health effects of cannabis and evidence on the social consequences of its prohibition described above. Third, the media framings affect politicians' understanding of the policy debate and the relevance of research evidence to it (Weiss, 1977, p. 18).

The cannabis policies that emerge often represent a compromise that will attract the support of key stakeholders with conflicting views. The strategies proposed for reducing cannabis use are often ones of modest effectiveness that will attract broad public support: media campaigns to discourage cannabis use among young people. Public education probably seems a "commonsense" response to politicians and the public and one that strongly appeals to the parents of adolescents.

Whither cannabis policy?

The chances of further cannabis law reform in countries like Australia, Canada and the United Kingdom have probably receded for a number of reasons.

First, the increasing evidence that cannabis use can adversely affect the health of some adolescents and young adults has been seen as undermining the simplest case for reform: that cannabis causes no harm. Such evidence is therefore interpreted politically as supporting the status quo. Second, the persuasive burden in policy

debates has accordingly been increased for advocates of cannabis law reform: they have to persuade the community that it is possible to change the law without increasing cannabis use and harm. Third, neurobiological research on the effects of cannabinoids on brain is also being interpreted as supporting the status quo. The policy inferences often implicitly drawn from this research (e.g. by Murray et al., 2007) are: that since cannabis produces effects on the brain like heroin and cocaine, it should be treated more like these drugs. These are not, of course, necessary policy consequences of neurobiological research on cannabis (see Iversen, 2007; Nutt, King, Saulsbury, & Blakemore, 2007) but they fit better with the prevailing policy framing in public debate. Fourth, increasing restrictive policies towards tobacco will probably make it harder to argue for more liberal policies towards cannabis smoking. Recent calls for a de facto prohibition on smoked tobacco (Bonnie, Stratton, & Wallace, 2007; Henningfield et al., 1998), for example, will make it harder to argue that we should legalise cannabis, unless non-smoked methods of delivery can be developed.

Conclusions

Cannabis adversely affects some users, especially adolescents who initiate use and young adults who become regular users. This pattern of use probably increases risks of motor vehicle crashes, cannabis dependence, adverse effects on the respiratory and cardiovascular systems, psychosis, and poorer educational outcomes and increased likelihood of using other illicit drugs in adolescence. This evidence tends to support the policy status quo because the policy debate has been simplified to a choice between the views that either cannabis use is harmless and so should be legalised or cannabis use is harmful and so should be prohibited. The conservative trend in cannabis policy in countries with hitherto more liberal cannabis policies, such as Australia, is likely to be reinforced by the popular interpretation of research on neurobiology of cannabinoids and by increasingly restrictive policies towards the other widely smoked drug, tobacco.

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Conflict of interest

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