

## COMPREHENSIVE REVIEW

# Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs

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### Abstract

*We outline and evaluate competing explanations of three relationships that have consistently been found between cannabis use and the use of other illicit drugs, namely, (1) that cannabis use typically precedes the use of other illicit drugs; and that (2) the earlier cannabis is used, and (3) the more regularly it is used, the more likely a young person is to use other illicit drugs. We consider three major competing explanations of these patterns: (1) that the relationship is due to the fact that there is a shared illicit market for cannabis and other drugs which makes it more likely that other illicit drugs will be used if cannabis is used; (2) that they are explained by the characteristics of those who use cannabis; and (3) that they reflect a causal relationship in which the pharmacological effects of cannabis on brain function increase the likelihood of using other illicit drugs. These explanations are evaluated in the light of evidence from longitudinal epidemiological studies, simulation studies, discordant twin studies and animal studies. The available evidence indicates that the association reflects in part but is not wholly explained by: (1) the selective recruitment to heavy cannabis use of persons with pre-existing traits (that may be in part genetic) that predispose to the use of a variety of different drugs; (2) the affiliation of cannabis users with drug using peers in settings that provide more opportunities to use other illicit drugs at an earlier age; (3) supported by socialisation into an illicit drug subculture with favourable attitudes towards the use of other illicit drugs. Animal studies have raised the possibility that regular cannabis use may have pharmacological effects on brain function that increase the likelihood of using other drugs. We conclude with suggestions for the type of research studies that will enable a decision to be made about the relative contributions that social context, individual characteristics, and drug effects make to the relationship between cannabis use and the use of other drugs.*

**Key words:** causal explanations of cannabis use, drug use patterns, gateway hypothesis.

### Introduction

Research on adolescent drug use over the past quarter century in the USA has consistently found that alcohol and tobacco are used before cannabis, which in turn, is used before hallucinogens and 'pills', and heroin and cocaine [1]. Some drugs in this sequence have been called 'gateway drugs': drugs whose use in some unspecified way is a cause of the use of later drugs in the sequence. Cannabis, for example, has been said to be a gateway drug for other illicit drugs [2] and alcohol and tobacco have been described as gateway drugs for cannabis use [2].

The gateway hypothesis has been one of the most controversial hypotheses in the epidemiology of drug

use. This has been in part because proponents and opponents of the hypothesis have not always been clear about what the hypothesis means and what policies it entails. Different explanations of the relationship between cannabis and other illicit drug use have affected drug policy in very different ways in different countries. In the USA, for example, health educators have argued that this pattern indicates that policy should aim to prevent or at least delay the use of cannabis in order to reduce the likelihood that young people will use other illicit drugs [3]. By contrast, drug policy analysts in the Netherlands have argued that the pattern is a consequence of the fact that cannabis and other illicit drugs are sold in the same black market under a policy of prohibition. They have decided that

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cannabis use should be decriminalised and retail sales of small quantities of cannabis should be tolerated in an effort to break the nexus between cannabis use and the use of other illicit drugs [4].

In this paper we review recent research that has been conducted on the ‘gateway hypothesis’. This includes a rich mix of study types that allow a clearer evaluation of the competing explanations of the gateway pattern of drug use in developed societies and the role that cannabis plays in that sequence. Before doing so we do three things. First we briefly summarise the type of relationships that have been consistently found between cannabis use and other types of illicit drug use that require an explanation. Second, we outline the major competing explanations that have been offered of the relationships. Third, we briefly discuss the type of evidence that is required to decide between these explanations.

### Gateway patterns of cannabis and other illicit drug use

Cross sectional surveys of adolescent drug use in the United States and elsewhere have consistently shown three types of association between cannabis use and the use of other illicit drugs, such as, heroin and cocaine [5].

First, American adolescents during the 1970s and 1980s showed a typical sequence of involvement with licit and illicit drugs in which almost all who tried cocaine and heroin had first used alcohol, tobacco and cannabis [1,6]. The exceptions to this generalisation have been found in samples of youth who live in inner city areas where a wide range of illicit drugs are readily available to young people [7].

Second, during the same period there was a strong relationship between *regular* cannabis use and the later use of heroin and cocaine. Kandel (1984), for example, found that only 7% of American youth who had never used cannabis reported using another illicit drug [8]. This figure increased to 33% among those who had used cannabis, and to 84% among current daily cannabis users. The same relationships have been observed in surveys of drug use in Australia [9].

Third, the earlier the age at which any drug was first used, the more likely the user was to use the next drug in the sequence [1,8,10–12]. So those who begin to use alcohol and tobacco at an early age were the most likely to use cannabis; early cannabis users, in turn, were more likely to use hallucinogens and ‘pills’ (amphetamines and tranquillisers); and early users of ‘pills’ were, in turn, the ones most likely to use cocaine and heroin.

These relationships between cannabis and heroin use have also been reported in longitudinal studies of drug use. One of the first such studies [13] followed up 222

African-American adolescents identified from school records until age 33 and interviewed them about their drug use in adolescence and young adulthood. They found that young men who had used cannabis before the age of 20 were more likely to use heroin than those who had not. These results have been confirmed in longitudinal studies by Kandel and her colleagues [14,15] in which drug use has been assessed in adolescents who have been followed into early adulthood [16–18]. These patterns of drug involvement have not been confined to the USA. In New Zealand, for example, studies of drug use in two birth cohorts [19–22] have found the same sequence of involvement with drugs and the same predictors of progression. In New Zealand cocaine and heroin are much less readily available than in the USA or Australia [21].

One feature of these patterns needs to be stressed: cannabis use per se is not a strong predictor of the use of other drugs. It is the *early initiation* and *regular use* of cannabis that are most strongly predictive of the use of other illicit drugs. These facts have implications for two common misinterpretations of the evidence. First, it is mistaken to believe (as the media is wont to do) that a young person who has experimented with cannabis on a small number of occasions is at high risk of using other illicit drugs. Second, contrary to many sceptics, the gateway hypothesis is *not* refuted by pointing out (as is true) that *most* cannabis users do not use other illicit drugs.

### Explanations of these ‘gateway’ patterns of drug use

MacCoun has provided a detailed typology of explanations of the gateway patterns of cannabis use [23] but for the sake of simplicity we classify these into three types of explanation. The first hypothesis is that there is no causal relationship between cannabis and other drug use; that the relationship arises because cannabis and other illicit drugs are supplied by the same black market, with the consequence that cannabis users have many more opportunities to try other illicit drugs than non-cannabis users. The second hypothesis is also that the relationship is not causal; the association is explained by characteristics of those who are early cannabis users that make them subsequently more likely to use other illicit drugs. The third hypothesis is that the relationship is causal because the pharmacological effects of cannabis increase an adolescent’s propensity to use other illicit drugs.

Each of these competing hypotheses will be evaluated in the light of the available evidence. Since there is no single piece of evidence that is decisive in choosing between the hypotheses we look for convergent support for the hypotheses from the findings of studies that use multiple methods of independent imperfection.

### **Making causal inferences from observational data**

The debate about whether cannabis is or is not a gateway drug turns upon the question of whether a causal relationship can be inferred from observational data. The application of standard criteria for causal inferences to this hypothesis would require: that there is an association between cannabis use and the use of other drugs; that chance is an unlikely explanation of the association; that cannabis use preceded the use of other drugs; and that plausible non-causal explanations of the association can be excluded (e.g. [24]).

There is abundant evidence of an association between cannabis use and other drug use which has been consistently replicated by investigators in different societies. This makes chance an unlikely explanation of the relationships between cannabis use and the use of other drugs. We also know from longitudinal studies that cannabis use usually precedes the use of other illicit drugs. The main debate about whether cannabis is a gateway drug therefore turns deciding between a causal interpretation of the association and hypotheses that attribute it to an unmeasured variable that is the cause of both cannabis use and other drug use, such as, the personal characteristics of users, or the shared illicit market for cannabis and other drugs.

An experiment in which persons were randomly assigned to use cannabis or not would provide the most convincing way of ruling out personal characteristics as a cause because random assignment would ensure that cannabis users and non-users did not differ prior to using cannabis use. This option is often not available because it would be unethical to force some adolescents to use cannabis, and impracticable to prevent those who were assigned not to use cannabis from doing so.

Experimentation with laboratory animals is the next best option. In such studies, mice, rats, or monkeys are randomly assigned to receive either cannabis or placebo and later given opportunities to self-administer other illicit drugs such as opioids and cocaine. The rates of self-administration could then be compared between the experimental and control animals. The gain in rigor is purchased at the cost of uncertainties about extrapolating findings across species when humans and animals use different routes of administration (e.g. oral and parenteral in animals versus smoked in humans), different forms of cannabis (pure THC in many animal studies versus smoked cannabis preparations in humans), and very different doses of THC (high doses in animals vs. typical long-term lower dosing of cannabis products smoked by humans).

The best human evidence comes from epidemiological studies that use statistical methods to rule out common causes in human studies. These involve using statistical methods to estimate the effects that cannabis use has on the likelihood of using other illicit drugs,

after adjusting for the effects of any differences between cannabis users and non-users that may affect the outcome (e.g. personal characteristics and life experiences before using cannabis). If the relationship persists after statistical adjustment, then confidence is increased that it is not attributable to the variables for which statistical adjustment has been made.

### *An overall appraisal of causal hypotheses*

Causal hypotheses are evaluated in the light of a body of research using criteria like those outlined by Hill [25]. These criteria are not sufficient for establishing that an association indicates a causal relationship but generally, the more of the criteria that are met, the more likely it is that the association is a causal one.

*Strength of association.* Stronger relationships are generally more deserving of trust than weaker ones that are more likely to be artefacts of measurement or sampling.

*Consistency.* Relationships which are consistently observed by different investigators, in different populations, using varied measures and research designs, are more credible than relationships which are not because this makes it unlikely that the relationship can be explained by design and sampling.

*Specificity.* Exists when cannabis use is strongly associated with other illicit drug use which is rare in non-cannabis users. If there is specificity we can be more confident that there is a causal relationship.

*Biological gradient.* Refers to a dose-response relationship between frequency and duration of cannabis use and the likelihood of using other illicit drugs.

*Biological plausibility.* If there is a plausible biological mechanism that would explain the relationship then its plausibility increases.

*Coherence.* Means that the relationship is consistent with the natural history and epidemiology of illicit drug use.

### *The social environmental hypothesis*

The pattern of illicit drug use among American adolescents in the 1970s was affected by drug availability [12]. Among cohorts of heroin users in the 1950s and 1960s, prior involvement with cannabis was rare outside geographic areas of the US in which it was readily available [26]. Research on African-American adolescents found that in these communities cocaine and heroin often preceded the use of the less readily available hallucinogens and 'pills' [12]. Similarly,

American soldiers in Vietnam were more likely to use heroin before they used alcohol because heroin was cheaper and more freely available in that setting than alcohol [27].

These historical and geographical variations in illicit drug use sequences suggest a sociological explanation of the higher rates of progression to heroin use among heavy cannabis users, namely that regular cannabis users are more likely to use other illicit drugs because they have more opportunities to do so than peers who do not use cannabis. Regular cannabis use, on this hypothesis, exposes cannabis users to opportunities to use other illicit drugs either through shared illicit markets or shared peer networks. Their drug using peers might also be expected to approve of other illicit drug use [26,28].

There have been few comparisons of ‘exposure opportunities’ between cannabis users and non-users. Fergusson and Horwood’s (2000) analysis of the Christchurch Child Development Study provided a limited assessment of the contribution made by self-reported affiliation with drug using peers to the relationship between cannabis and other illicit drug use [21]. They assessed the effects of self-reported peer use of alcohol, cannabis and other illicit drugs on the relationship between cannabis and other illicit drugs. The inclusion of peer drug use reduced but did not eliminate the relationship between cannabis and other illicit drug use.

Wagner and Anthony (2002) examined the effects of exposure opportunities to cannabis and other drugs on cannabis and other illicit drug use among young adults (aged 12 to 25 years) in the pooled 1991–1994 US National Household Surveys of Drug Abuse [29]. They assessed exposure opportunities by the age at which a respondent first reported an opportunity to use tobacco or alcohol, cannabis and cocaine. Wagner and Anthony found that young people who had used alcohol or tobacco were three times more likely to report an opportunity to use cannabis (75% vs 25%). They also had these opportunities at an earlier age than those who had not used alcohol or tobacco. Alcohol and tobacco users were also much more likely to use cannabis when the opportunity arose than young people who had not used alcohol or tobacco (85% vs < 25%). And they did so sooner than peers who had not (50% of alcohol and tobacco users had used cannabis within 1 year of first offer whereas fewer than 20% of non alcohol and tobacco users had used within 5 years of first offer). These relationships did not change when young people who had used within a year of first opportunity to do so were excluded from the analysis (to reduce the possibility that the relationship was due to active cannabis seeking by some young people).

Wagner and Anthony also found that opportunities to use cocaine were strongly related to cannabis,

alcohol and tobacco use. Only 13% of young people who had not used alcohol, tobacco or cannabis reported an opportunity to use cocaine. This compared with 26% of alcohol and tobacco users, 51% of cannabis only users; and 75% of those who had used alcohol, tobacco and cannabis. Those who had used cannabis were 15 times more likely to accept an offer to use cocaine than those who had not. These relationships did not change when young people who used cocaine within a year of their first opportunity to use were excluded from the analysis. This provides the most direct evidence to date that drug use influences the opportunity to use and the likelihood of accepting the opportunity presumably provided within one’s peer group. Because no measures of propensity to use illicit drugs were included these data do not enable personal characteristics to be excluded as an explanation of the associations.

### **The effects of cannabis decriminalisation on gateway patterns**

If one accepts the social environmental explanation of the gateway pattern then an obvious policy implication is that we should break the nexus between cannabis and other illicit by separating the markets for cannabis and other drugs [28]. If the relationship arises because of shared drug markets then the separation of cannabis and other illicit drug markets should substantially reduce (if not abolish) the associations between cannabis and other illicit drug use. A conspicuous absence from the literature on the gateway hypothesis is any research using longitudinal or twin study designs to evaluate the effects of Dutch cannabis policy on the relationship between cannabis use and the use of other illicit drugs, such as cocaine and heroin. Given the rationale for Dutch cannabis policy, the lack of rigorous testing of its effects represents a lost opportunity to evaluate the effects of a widely advocated harm reduction measure. We hope that in future opportunities will be taken to test the effects of Dutch policy using data from large cohorts of young adults in the Netherlands (e.g [30]) and from Dutch twin studies (e.g. [31]).

### **Is the gateway pattern explained by personal propensities to use drugs?**

According to this hypothesis it is the personal characteristics of the individuals who use cannabis that also make them more likely to use other drugs. These characteristics might be individual propensities to engage in socially deviant conduct, such as, drug use, criminal acts and precocious sexual activity. Such propensities could be of environmental origin, or they could be due to a shared genetic vulnerability to

develop different types of drug dependence, or they could be due to some combination of the two.

A plausible explanation of the association between regular cannabis use and the use of other drugs is that there is selective recruitment to early cannabis use of socially deviant young people who have a predilection to use a variety of drugs including alcohol, cannabis, cocaine and heroin [21]. The sequence of drug involvement, on this hypothesis, reflects the differing availability and societal disapproval of different types of drug use [10]. Alcohol and tobacco use precede cannabis use because alcohol and tobacco are more readily available to adolescents and their use by adults is more socially approved than that of cannabis. Cannabis use precedes heroin use for the same reasons. On this hypothesis, cannabis use does not cause the use of other illicit drugs; rather, cannabis and heroin use are common consequences of pre-existing propensities to use all drugs [16,32].

The selective recruitment hypothesis is supported by the substantial correlations between nonconforming adolescent behaviours, such as, dropping out of high school, early premarital sexual experience and pregnancy, delinquency, and early alcohol and illicit drug use [33,34]. All of these are correlated with nonconformist and rebellious attitudes and with antisocial conduct in late childhood [35] and early adolescence [32,33]. Regular cannabis users are more likely than their peers: to have a history of such antisocial behaviour [22,36]; to be nonconformist and alienated [35–37]; to perform poorly at school [38–40]; and to use drugs to deal with personal distress [35,41]. The more of these risk factors that adolescents have, the more likely they are to use cannabis and other drugs [36,42,43].

The selective recruitment hypothesis has been tested in longitudinal studies by assessing whether cannabis use predicts the use of heroin and cocaine after statistically controlling for differences between cannabis users and nonusers in personal characteristics that preceded their cannabis use [21]. Yamaguchi (1984), for example, found that the relationship between cannabis use and ‘harder’ illicit drug use was reduced but it still persisted after statistically controlling for pre-existing adolescent behaviours and attitudes, interpersonal factors, and the age of initiation into drug use [17]. They interpreted this as evidence that the relationship between cannabis use and the use of other illicit drugs was causal. The same finding has emerged in other studies [13,14,44].

Fergusson and colleagues (1997, 2000, 2002) have reported one of the most comprehensive tests of the hypothesis in a prospective study of 990 New Zealand children who were followed from birth to age 21 years and regularly assessed on a large set of potentially confounding psychosocial variables [19,21,45]. These

variables included: family background (socio-economic status, parental conflict and divorce, childhood sexual abuse, parental punishment and parental attachment); parental adjustment (parental alcohol and drug problems, criminality and illicit drug use); individual characteristics of the young person (gender, intelligence, novelty seeking); early adolescent development (cigarette smoking, frequency of alcohol use, juvenile offending, dropping out of school, conduct problems and attitudes towards drug use); peer affiliations (peer use and problems with alcohol and other drug use); and personal history of risk taking.

Fergusson and Horwood (1997) found a strong dose response relationship between the frequency of cannabis use by age 16 (no use, use less than 10 times and use more than 10 times) and development of a problem with cannabis, alcohol or other substances by age 18 [19]. There was also a strong association between the social background of the adolescents and their likelihood of having used cannabis by age 16. Early cannabis users came from lower socio-economic status families with a history of parental conflict, parental criminality, alcohol and drug use, and low parental attachment. They also had a history of conduct problems, low self-esteem and high novelty seeking, and were likely to affiliate with delinquent peers. Adjustment for these family and personal factors substantially reduced but did not eliminate the relationships between early cannabis use and the use of other illicit drugs.

Fergusson and Horwood (2000) reported similar analyses in a subsequent follow up of the birth cohort [21]. They found that 69% of their sample reported using cannabis by age 21 and just over a quarter had used other illicit drugs, although only 4% had used cocaine or opiates. They found a strong dose-response relationship between the number of times that cannabis had been used at any age and the later risk of using another illicit drug. Those who had used cannabis once or twice were 3.5 more likely to have used other illicit drugs: the risks were 12.0 times higher for those who had used 3 to 11 times, 41.3 for those who had used 12 to 49 times and 142.8 for those who had used 50 times or more.

The strength of the relationship between frequency of cannabis use and the use of other illicit drugs was reduced after statistically controlling for confounding factors. Nonetheless, the relationships showed the same dose-response relationship, namely, 2.8 for those who had used once or twice, 7.7 for those who had used 3 to 11 times, 21.3 for those who had used 12 to 49 times and 59.2 for those who had used for 50 times or more. These findings suggest that the selective recruitment hypothesis is unlikely to wholly explain the association between cannabis use and other illicit drug use.

Fergusson, Horwood and Swain-Campbell (2002) have replicated these results in further analyses of the cohort at age 21 using a more sophisticated form of statistical analysis [45]. They used fixed effects regression methods to control for the effects of unobserved individual differences in propensity to use other drugs between early and late cannabis users. They also found a dose response relationship between cannabis use and the risk of using other illicit drugs that varied with the age of first cannabis use: the earlier that cannabis was first used, the higher was the risk of using other illicit drugs.

These studies suggest two important things. First, selective recruitment explains part of the relationship between cannabis and other illicit drug use. Cannabis users differ from non-users in a variety of ways (before they use cannabis) that make them more likely to use other illicit drugs. Controlling for these factors reduces the strength of the association, indicating that some part of the association can be explained by selective recruitment. Nonetheless, the fact that the association persists after controlling for these factors provides support for some type of causal relationship between cannabis and other illicit drug use.

The results of these epidemiological studies would seem to have largely undercut the common cause explanation of the gateway pattern of drug use. A recent study, however, has provided some support for the common cause hypothesis. Morral *et al* (2002) reported a simulation study that modelled a common cause hypothesis of the association between cannabis use and the use of other illicit drugs [5]. They asked whether a common cause model would reproduce the three types of relationship described above, namely, that cannabis users have a higher risk of trying harder drugs; that cannabis use precedes the use of other illicit drugs; and that there is a dose response relationship between the frequency of cannabis use and the risk of using other illicit drugs.

The common factor model that Morral *et al* tested assumed that individuals only differ in their propensity to use a variety of drugs. They did not make any specific assumptions about the nature of this propensity, allowing that it could reflect personal characteristics, peer group drug use and the availability of drugs in individuals' neighbourhoods or some combination of these. They only assumed that the propensity to use drugs was correlated with the opportunity to use them and with the age of first use of any drug. Critically, their model assumed that there was *no* correlation between (1) the opportunities to use or age of first use of cannabis and (2) the opportunities to use or age of first use of other illicit drugs.

Morral *et al*'s common cause model reproduced all three 'gateway' patterns. Cannabis users were more likely to use harder drugs; cannabis use preceded the

use of other illicit drugs, and there was a dose response relationship between the frequency of cannabis use and the use of other illicit drugs.

Morral *et al* also questioned the effectiveness of the common strategy for testing the common factor model, namely, testing if relationships between cannabis use and other drugs persist after controlling for indicators of the pre-existing propensity to use cannabis and other drugs (e.g. [21]). Their data suggested that this research strategy was only successful if the indicators were perfectly correlated with the propensity to use cannabis and other drugs. When the indicators were less than perfectly reliable, there were still spuriously high associations between cannabis use and the use of other illicit drugs after statistically controlling for the indicators. This criticism has more limited force in the case of the most recent study by Fergusson and colleagues which used fixed effects regression to control for unmeasured variables.

#### *A shared genetic vulnerability to drug dependence*

Behaviour genetic studies suggest another common causal explanation of the association between cannabis and other illicit drug use, namely, a shared genetic vulnerability to develop dependence on a range of different drugs. A substantial number of studies of identical and non-identical twins indicate that there is a genetic vulnerability to developing dependence on alcohol [46], cannabis [47] and tobacco [48]. More recent studies suggest that a substantial part of the genetic vulnerability to dependence on these three drugs is shared, as are the family and environmental factors that influence alcohol and cannabis dependence [49]. The genetic contribution to dependence on 'harder' drugs is less certain because rates of use in these twin studies have been low but the same shared genetic factors also appear to be involved [50].

Lynskey *et al* (2003) have recently used twin study methods to test the hypothesis that the association between cannabis and other illicit drug use can be explained by shared genes and environment [51]. They examined the relationship between cannabis and other illicit drug use in 136 monozygotic and 175 dizygotic Australian twin pairs in which one twin had, and the other twin had not, used cannabis before the age of 17 years. This study provided a strong test of a common cause hypothesis, whether this was shared susceptibility genes, shared environment (e.g. the family in which the twins grew up) or some combination of shared genes and environment. 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 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 age 17.

Lynskey *et al* found that the twin who had used cannabis before age 17 was more likely to have used sedatives, hallucinogens, stimulants and opioids than their co-twin who had not. 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. They also persisted when the analysis was confined to twin pairs in which both had used cannabis at some time in their lives.

The findings of Lynskey *et al* 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 [21]. 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) [21] but this may reflect the cruder measure of cannabis use used in the Lynskey study (user or non user rather than the ordinal scale of increasing frequency of use used in the Fergusson *et al* study).

### Testing pharmacological explanations of the gateway pattern

According to the hypothesis that the pharmacological effects of cannabis use predisposes regular cannabis users to use other illicit drugs [52, 53], cannabis use produces changes in the brain that sensitise cannabis users to the euphoric effects of other drugs. Nahas (1990), for example, hypothesised that ‘the biochemical changes induced by marijuana in the brain result in a drug-seeking, drug-taking behaviour, which in many instances will lead the user to experiment with other pleasurable substances’ (p. xxiii), [52]).

Animal studies suggest a number of plausible mechanisms by which cannabis use could increase the likelihood of using other illicit drugs. First, animal studies (e.g. [54]) indicate that common neural pathways underlie the rewarding effects of cannabis, cocaine, heroin and nicotine [23]. All of these drugs act on the dopaminergic neurotransmitter systems that are involved in the ‘reward centres’ in the midbrain, the nucleus accumbens [55]. Second, animal studies indicate that the cannabinoid and opioid systems in the brain interact with each other, influencing each others’ analgesic and euphoric effects, and producing similar effects on dopaminergic systems in the midbrain [54,56]. Third, mutant mice in which the CB<sub>1</sub> cannabinoid receptor had been knocked out found

opioids less rewarding than rats with CB<sub>1</sub> receptors [57]. Fourth, studies indicate that the corticotropin-releasing factor which is involved in producing withdrawal symptoms from alcohol, opioids, and cocaine is also released when rats trained to self-administer cannabinoids are treated with a cannabinoid antagonist [58].

Animal studies also potentially provide a rigorous way of directly testing whether these neural mechanisms may explain the relationship observed between cannabis and other illicit drug use in humans. Specifically, animal studies may reveal whether self-administration of cannabinoids ‘prime’ animals to self-administer other illicit drugs when given the opportunity [59]. Two recent animal studies [60,61], for example, have examined cross-sensitivity between cannabinoids and opioids and stimulant drugs in rats. They provided some evidence for cross-sensitivity between cannabinoids and opioids, although in one study this was only observed in a strain of rats that were highly responsive to drug effects [61]. More studies of this type would be useful.

There are a number of uncertainties about the relevance of these studies to gateway patterns of adolescent drug use. First, these effects were produced by injecting high doses of cannabinoids whereas most adolescents smoke cannabis. They may be most relevant to the minority of adolescents who use cannabis very heavily; this group would expose themselves to similar doses of THC [62]. Second, the cross-sensitisation between cannabinoids and opioids was symmetrical: that is, animals who were administered opioids were cross-sensitive to cannabinoids and vice versa [60]. This suggests that if opioids were more readily available than cannabis, then opioids would be a gateway to cannabis use.

### The effects of delaying gateway drug use

If cannabis use causally contributes to the increased use of other illicit drugs then we should, in principle, be able to reduce the use of other illicit drugs by delaying or preventing adolescent cannabis use (e.g. [3]). If this hypothesis was correct then programs that delayed the use of alcohol, tobacco and cannabis should reduce rates of other illicit drug use. Most prevention studies have evaluated programs that aim to prevent tobacco use and to delay alcohol use, the most widely used drugs in adolescence. These studies have provided some suggestive evidence that preventing or delaying tobacco and alcohol use reduces rates of cannabis use [63].

There are several good reasons why no studies to date have demonstrated that delaying cannabis use reduces the use of other illicit drugs. First, many preventive programs that address illicit drug use have not been evaluated, and among those programs that

have been evaluated, it has proven difficult to demonstrate that prevention programs have an effect on the use of less commonly used illicit drugs [64,65]. Second, if the gateway hypothesis is correct, even the most effective prevention programs would produce very modest reductions in the use of other illicit drugs. This is because their impacts on cannabis use are modest and because other illicit drug use is a rarer event in representative samples of youth [66]. Third, very large sample sizes are consequently required to provide adequate statistical power to detect any effect that delaying cannabis use may have on the use of other illicit drugs.

### An overall evaluation

The evidence for a causal relationship between cannabis use and other illicit drug use can be evaluated against Hill's criteria. There is a reasonably *strong* association between *regular and early* cannabis use and other illicit drug use. It has been *consistently* observed over 30 years in the USA and other developed societies. There is a fair degree of *specificity* in that cannabis use is more strongly associated with other illicit drug use than either alcohol or tobacco use. There is a *biological gradient* or dose-response relationship in that it is young people who are the earliest and most frequent cannabis users who are the most likely to use other illicit drugs.

Animal studies provide some support for *biological plausibility* in providing a number of biological mechanisms that could explain the relationship between cannabis and other types of illicit drug use, namely, that all of these drugs act on the same dopamine mediated reward systems in the brain; that cannabinoids and opioids interact with each other and show cross-tolerance; and that similar mechanism may underlie the experience of withdrawal symptoms from all of these drugs. The results are broadly *coherent* with the natural history and epidemiology of cannabis and other illicit drug use.

Nonetheless, the role of cannabis in the 'gateway pattern' of drug use remains controversial because of the difficulty of excluding the hypothesis that the gateway pattern can be explained by the common characteristics of those who use cannabis and other drugs. The finding of a simulation study that supported the common causal explanation has to be weighed against (1) a number of well controlled longitudinal studies which suggest that selective recruitment to cannabis use does not wholly explain the association between cannabis use and the use of other illicit drugs; and (2) a discordant twin study which suggests that shared genes and environment do not wholly explain the association.

We believe that it will be possible to make an informed choice between a causal and the competing common causal explanations of the gateway pattern can

be made in the light of the coherence of the outcomes of four types of research: (1) animal tests of pharmacological hypotheses provided that these can be done under conditions that plausibly resemble patterns of cannabis use among young adults; (2) large, well designed intervention studies which test whether preventing or delaying the onset of cannabis use reduces the use of other illicit drugs; (3) more behaviour genetic studies using the discordant twin design to test the roles of shared genes and environment as explanations of the co-occurrence of cannabis and other types of illicit drug use; and (4) more rigorous tests (using discordant twin designs and longitudinal epidemiological studies) of the effects that Netherlands drug policy has had on the association between regular cannabis use and the use of other illicit drugs.

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